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(54) Title: HYBRIDIZATION STATION

(57) Abstract: This invention provides a station for rapidly preparing arrayed slides for hybridizations. At least one micro-arrayed slide is inserted into a carrier. A hybridization chamber is formed by a chamber element contacting the slide. The carrier is removably insertable into the station for the carrying out of various steps associated with the pre-hybridization and post-hybridization processes. The station generally includes at least one wash station assembly, a fluid delivery system, a sample delivery system, and a temperature control system.

HYBRIDIZATION STATION

CROSS-REFERENCE TO RELATED APPLICATIONS

The present application is related to and claims priority from Provisional Patent Application entitled "Drug Discovery (NDD) Instrumentation Based on Laser Capture Microdissection (LCM) and cDNA Gene Expression Array Technologies", Serial No. 60/163,634, filed November 4, 1999, and is incorporated in its entirety into the present application herewith.

FIELD OF THE INVENTION

The present invention relates to a hybridization station and, more particularly, to a hybridization station having a hybridization chamber for rapidly performing repeated hybridizations.

BACKGROUND

Nucleic acid hybridizations generally utilize arrays of oligonucleotide sequences immobilized on solid supports to detect complementary nucleic acid sequences in an assayed sample. The arrays can be used to determine the complete sequence of the assayed nucleic acid and to detect the presence of a nucleic acid with a specific nucleotide sequence. A wide variety of applications are possible including sequencing-by-hybridization techniques and diagnostic methods for monitoring differential gene expression and detecting genetic and other disorders.

One consideration in nucleic acid hybridizations is the rate and stringency at which the hybridization reaction occurs. The hybridization rate and stringency can be affected by a variety of conditions. One such condition is the temperature of the hybridization reaction. Hybridizations occur at a fixed and very critical temperature. During the hybridization process, it is required that hybridization solution be introduced to the hybridization chamber at a specific temperature. Conventional hybridization chambers do not allow for introducing hybridization solution into the chamber while incubated at a specific temperature. Such conventional chambers often require that the chamber be removed from

the heat source, hybridized and then returned to the heat source. Therefore, conventional hybridization chambers can often result in significant temperature differences within the chamber during the hybridization process. These temperature differences can be problematic. In addition, the above-mentioned factors also apply to rather elaborate wash procedures that follow hybridization.

Other conditions that affect the hybridization rate include the concentration of the target nucleic acid in the sample, the composition of the hybridization solution, and the level of mixing of the target nucleic acid during the hybridization. Insufficient mixing can result in slower binding rates of probe to target.

Given these numerous conditions that affect the rate of the hybridization reaction it is desirable to provide integrated devices that are capable of optimizing a number of the specific conditions of these hybridization reactions. In particular, a hybridization station that is capable of rapidly and repeatedly delivering a sample onto an array, mixing the sample during hybridization, maintaining the sample at an optimal temperature for hybridization, removing the sample from the chamber following hybridization, and washing the array is desirable.

SUMMARY OF THE INVENTION

In accordance with one aspect of the invention, there is provided a chamber for performing hybridization reactions. The chamber includes an examination surface and a chamber element. The chamber element has an inner surface and a raised portion defining an interior. The raised portion extends from the inner surface. The chamber is formed by the chamber element contacting the examination surface such that the raised portion engages the examination surface. The chamber is defined by the examination surface and the interior wherein the inner surface of the interior is spaced from the examination surface.

In accordance with another aspect of the invention, there is provided a carrier. The carrier includes at least one chamber. The chamber is formed by a chamber element contacting an examination surface. The chamber element has an inner surface and a raised portion extending from the inner surface. The inner surface of the chamber element, that is encompassed by the raised portion, is spaced from the examination surface by the raised portion.

In accordance with yet another aspect of the invention, there is provided a hybridization method. The method includes providing a hybridization station having a carrier and a wash station. The carrier is removably insertable into the wash station. At least one slide having sample coupled to an examination surface is loaded into the carrier. A chamber element is provided. The chamber element is disposed in the carrier and the chamber element has an inner surface and a raised portion extending from the inner surface. The chamber element has at least one orifice. The at least one chamber element is located over the at least one slide to form a chamber such that the raised portion contacts the slide and the inner surface, that is encompassed by the raised portion, is spaced from the examination surface. The raised portion contacts the slide such that fluid does not cross the raised portion. The carrier is loaded into the wash station and fluid is injected into the chamber through the at least one orifice.

In accordance with another aspect of the invention, there is provided a method. The method includes inserting at least one first carrier into a hybridization station. The at least one first carrier has at least one chamber. A solution is injected into the at least one chamber of the first carrier. The at least one first carrier is removed from the hybridization station to free the hybridization station for receiving at least one second carrier. The at least one second carrier has at least one chamber. The at least one second carrier is inserted into the hybridization station.

In accordance with another aspect of the invention, there is provided a carrier removably insertable into a hybridization station. The carrier includes at least one chamber. The chamber has a first surface and a second surface. The second surface has a side wall extending from the second surface. The side wall of the second surface contacts the first surface and encompasses sample coupled to the first surface. A portion of the second surface that is encompassed by the side wall being spaced from the first surface.

In accordance with another aspect of the invention, there is provided a hybridization station. The hybridization station includes at least one wash station assembly and a fluid delivery system coupled to the wash station assembly. The hybridization station further includes a sample delivery system adapted for fluid communication with the wash station assembly. A temperature control system in thermal communication with the wash station assembly is also included. A controller is coupled to the fluid delivery system.

BRIEF DESCRIPTION OF THE DRAWINGS

The foregoing and other advantages of the invention will become apparent upon reading the following detailed description and upon reference to the drawings in which:

FIG. 1 is a perspective view of the hybridization station of the present invention;

FIG. 2 is a perspective view of the wash station assembly of the present invention;

FIG. 3 is an exploded view of the wash station assembly of the present invention;

FIG. 4 is a perspective view of the carrier assembly of the present invention;

FIG. 5 is an exploded view of the carrier assembly of the present invention;

FIG. 6 is a perspective view of the carrier base assembly of the present invention;

FIG. 7 is a perspective view of the carrier base of the present invention;

FIG. 8 is a top view of the carrier base of the present invention;

FIG. 9 is a cross-section view along line 9-9 of FIG. 8 of the carrier base of the present invention;

FIG. 10 is a side elevational view of a latch pin of the present invention;

FIG. 11 is a top view of the lower pad of the present invention;

FIG. 12 is a top view of the slide locator of the present invention;

FIG. 13 is a perspective view of the carrier top assembly of the present invention;

FIG. 14 is a perspective view of the carrier top of the present invention;

FIG. 15 is a bottom view of the carrier top of the present invention;

FIG. 16 is a partial sectional view along line 16-16 of FIG. 14 of the carrier top of the present invention;

FIG. 17 is a detailed view of the partial cross section of FIG 16 of the carrier top of the present invention;

FIG. 18 is a top view of the top pad of the present invention;

FIG. 19 is a top view of the chamber element of the present invention;

FIG. 20 is a side elevational end view of the chamber element of the present invention;

FIG. 21 is a bottom view of the chamber element of the present invention;

FIG. 22 is a cross-sectional view along line 22-22 of FIG. 21 of the chamber element of the present invention;

FIG. 23 is a detailed view of the cross-section of FIG. 22 of the chamber element of the present invention;

FIG. 24 is perspective view of the carrier clamp assembly of the present invention;

FIG. 25 is a perspective view of the first hook assembly of the present invention;

FIG. 26 is a perspective view of the wash station assembly of the present invention with the carrier assembly removed;

FIG. 27 is a perspective view of the needle assembly of the present invention;

FIG. 28 is a perspective view of the needle frame of the present invention;

FIG. 29 is a cross-sectional view of the needle tube of the present invention;

FIG. 30 is a perspective view of the guide pin of the present invention;

FIG. 31 is a cross-sectional view of the guide pin of the present invention;

FIG. 32 is an exploded view of the needle system of the present invention;

FIG. 33 is a perspective view of a needle system of the present invention;

FIG. 34 is a perspective view of the needle assembly and a portion of the frame structure of the present invention; and

FIG. 35 is a schematic of the fluid delivery system and the sample delivery system of the present invention.

While the invention is susceptible to various modifications and alternative forms, specific variations have been shown by way of example in the drawings and will be described herein. However, it should be understood that the invention is not limited to the particular forms disclosed. Rather, the invention is to cover all modifications, equivalents, and alternatives falling within the spirit and scope of the invention as defined by the appended claims.

DETAILED DESCRIPTION

Referring now to FIG. 1, a hybridization station 10 in accordance with the present invention is illustrated. Hybridization is a process well known to those of ordinary skill in the art. The hybridization station 10 is generally used for performing hybridization reactions such as hybridizing a sample of nucleic acids to an array of nucleic acid probes; however, it is understood by those skilled in the art from this disclosure that the hybridization station 10 could be used for other purposes such as staining a tissue sample, washing a hybridization array or a stained slide, recovering sample from a hybridization array, recovering stain from a stained slide, and the like without departing from the spirit and scope of the invention. For example, a variety of reactions may be performed using the

hybridization station 10 of the present invention including extension or amplification reactions using tethered probes as template or primer sequences, screening of receptors against arrays of small molecules, peptides or peptidomimetics, polymerase chain reactions with primer and template in solution, and the like.

The hybridization station 10 includes at least one wash station assembly 12, a fluid delivery system 14, a sample delivery system 16, a temperature control system 18, and a process controller 20. Although the hybridization station 10 of FIG. 1 illustrates two wash station assemblies 12, the invention is not so limited. Because the wash station assemblies 12 are substantially identical only one wash station assembly 12 will now be described.

A wash station assembly 12 is shown in FIG. 2 and an exploded view of the wash station assembly 12 is shown in FIG. 3. The wash station assembly 12 includes a carrier assembly 22, a needle assembly 24, and a frame structure 26.

Referring now to FIGs. 4 and 5, the carrier assembly 22 or cassette includes a carrier base assembly 28, a carrier top assembly 30, and a carrier clamp assembly 32. The carrier base assembly 28 and the carrier top assembly 30 are removably joined via the carrier clamp assembly 32. The carrier base assembly 28 is shown in FIG. 6. The carrier base assembly 28 includes a carrier base 34, a lower pad 36, and a slide locator 38.

Referring now to FIGs. 7-9, there is shown a carrier base 34. The carrier base 34 is substantially a rectangular block comprising stainless steel or any other suitable material. The carrier base 34 is approximately 9.0 inches in length, approximately 4.0 inches in width and approximately 0.4 inches in thickness. The carrier base 34 includes a top 40, a bottom 42, a first side wall 44, a second side wall 46, a first end wall 48 and a second end wall 50. The first and second side walls 44, 46 and the first and second end walls 48, 50 extend upwardly from the bottom 42 towards the top 40. A plurality of slide apertures 52 are defined in the carrier base 34. The slide apertures 52 are dimensioned slightly smaller than a standard slide 53. In particular, the slide apertures 52 are approximately 0.80 inches wide and approximately 2.20 inches in length; whereas, a standard slide is approximately 1.0 inches in width and approximately 3.0 inches in length. Although the carrier base 34 is shown with six slide apertures 52, the invention is not so limited and any number of slide apertures 52 are within the scope of the invention.

A plurality of locator bores 54 are defined in the top 40 of the carrier base 34. In addition to the plurality of locator bores 54, two male-member bores 56, each for receiving

a male member 58, as shown in FIG. 6, are defined in the top 40 of the carrier base 34. Also, two female-member bores 60, each for receiving a female member 62, are defined in the top 40 of the carrier base 34. A recess 64 is defined in the bottom 42 of the carrier base 34 for easily accessing the slide apertures 52.

A first side cut 66 is defined in the first end wall 48 of the carrier base 34. The first end wall 48 of the carrier base 34 includes a first latch pin bore 68 for receiving a latch pin 70. The first latch pin bore 68 is defined in a location of the first side cut 66. A second side cut 72 is defined in the second end wall 50 of the carrier base 34. The second end wall 50 of the carrier base 34 includes a second latch pin bore 74 for receiving a latch pin 70. The second latch pin bore 74 is defined in a location of the second side cut 72.

A latch pin 70 is shown in FIG. 10. The latch pin is generally cylindrical and defines a groove 76. Latch pins 70 are insertable into the latch pin bores 68, 74 of the first and second end walls 48, 50 such that the groove 76 of the latch pin 70 is exposed and directed away from the top 40 and towards the bottom 42 of the carrier base 34.

Referring now to FIG. 11 there is shown a lower pad 36. The lower pad 36 is made of resilient silicone material for cushioning the slides 53, however, any suitable material may be employed for the lower pad 36 to achieve the same effect. The lower pad 36 is generally rectangular in shape having a length of approximately 7.5 inches, a width of approximately 4.0 inches and a thickness of approximately 0.031 inches. A plurality of slide apertures 80 are defined in the lower pad 36. The slide apertures 80 of the lower pad 36 are dimensioned slightly smaller than a standard slide 53. In particular, the slide apertures 80 of the lower pad 36 are approximately 0.800 inches wide and approximately 2.20 inches in length; whereas, a standard slide 53 is approximately 1.00 inches in width and approximately 3.00 inches in length. Although the lower pad 36 is shown with six slide apertures 80, the invention is not so limited and any number of slide apertures 80 are within the scope of the invention. In addition to the slide apertures 80, a plurality openings 82 are defined in the lower pad 36 adjacent to the slide apertures 80. Also, a plurality of locator apertures 84 are defined in the lower pad 36.

Referring now to FIG. 12, there is shown a slide locator 38 of the carrier base 34. The slide locator 38 is a generally rectangular sheet approximately 7.50 inches in length, approximately 4.00 inches in width and approximately 0.02 inches in thickness. The slide locator 38 is made of stainless steel; however, any suitable material may be employed. A

plurality of slide apertures 86 are defined in the slide locator 38. Each of the slide apertures 86 of the slide locator 38 are dimensioned to have substantially the same size as a standard slide 53. In particular, the slide apertures 86 of the slide locator 38 are approximately 1.0 inches wide and approximately 3.0 inches in length. Although the slide locator 38 is shown with six slide apertures 86, the invention is not so limited and any number of slide apertures 86 are within the scope of the invention. The slide apertures 86 in the slide locator 38 serve to position each slide 53 in a desired location on the carrier base 34. In addition to the slide apertures 86, a plurality of locator apertures 88 are defined in the slide locator 38.

As shown in FIG. 5, to assemble the carrier base assembly 28, the slide apertures 52 of the carrier base 34, the slide apertures 80 of the lower pad 36, and the slide apertures 86 of the slide locator 38 are all aligned. Also, locator apertures 84 of the lower pad 36 and the locator apertures 88 of the slide locator 38 are aligned with the locator bores 54 of the carrier base 34. Locator fasteners 90, as shown in FIGs. 5 and 6, are passed through the locator apertures 84 in the lower pad 36, the locator apertures 88 in the slide locator 38 and threaded into the locator bores 54 of the carrier base 34 to secure the slide locator 38 and lower pad 36 to the carrier base 34.

Male members 58 are inserted into the male member bores 56 and female members 62 are inserted into the female member bores 60. To substantially complete the assembly of the carrier base 34, latch pins 70 are inserted into the latch pin bores 68, 74 of the first and second end walls 48, 50 such that the groove 76 of each latch pin 70 is exposed and directed away from the top 40 and towards the bottom 42 of the carrier base 34.

The carrier top assembly 30 includes a carrier top 92, a top pad 94, chamber element 96, and a carrier clamp assembly 32 as shown in FIG. 13. A carrier top 92 is illustrated in FIGs. 14-17. The carrier top 92 is substantially a rectangular block comprising aluminum or any other suitable material. The carrier top 92 is approximately 9.0 inches in length, approximately 4.0 inches in width, and approximately 0.40 inches in thickness. The carrier top 92 includes a top 98, a bottom 100, a first side wall 102, a second side wall 104, a first end wall 106, and a second end wall 108. The first and second side walls 102, 104 and the first and second end walls 106, 108 extend upwardly from the bottom 100 of the carrier top 92 towards the top 98 of the carrier top 92. The top 98 includes a recess 110 and mounting features 111 for receiving a clamp assembly 32. A first

side cut 112 is defined in the first end wall 106 of the carrier top 92. A second side cut 114 is defined in the second end wall 108 of the carrier top 92.

A plurality of flow apertures 116 are defined in the carrier top 92. For a carrier assembly 22 having a capacity of six standard slides 53, twelve flow apertures 116 are defined in the carrier top 92; however, the invention is not so limited and any optimal number of flow apertures 116 are within the scope of the invention. The flow apertures 116 are generally cylindrical in shape. As shown in FIG. 16 and 17, the flow apertures 116 have a tapered end 118 such that the diameter of a flow aperture 116 at the bottom 100 of the carrier top 92 is approximately 0.125 inches and the diameter of the flow aperture 116 at the top 98 of the carrier top 92 is approximately 0.179 inches.

Adjacent to each flow aperture 116, a chamber locator bore 120 is defined. The chamber locator bore 120 is designed for receiving a chamber pin (not shown) for securing the chamber element 96 to the carrier top 92. A plurality of pad locator bores 122 are defined in the bottom 100 of the carrier top 92. Also, two female-member bores 126, each for receiving a female member 128, as shown in FIG. 13, are defined in the bottom 100 of the carrier top 92.

A top pad 94 is illustrated in FIG. 18. The top pad 94 is made of urethane foam for cushioning the slides, however, any suitable material may be employed for the top pad 94. The top pad 94 is substantially rectangular in shape having a length of approximately 8.25 inches, a width of approximately 2.765 inches, and a thickness of approximately 0.64 inches. A plurality of slide apertures 132 are defined in the top pad 94. The slide apertures 132 of the top pad 94 are dimensioned slightly smaller than a standard slide 53. The top pad 94 further includes a plurality of pad locator apertures 134.

A plurality of flow apertures 136 are also defined in the top pad 94 adjacent to the slide apertures 132. A pair of flow apertures 136 are positioned adjacent to each slide aperture 132 of the top pad 94. The flow apertures 136 of the top pad 94 are substantially coincident with the flow apertures 116 of the carrier top 92. In addition to the flow apertures 136, a plurality of chamber locator apertures 138 are formed in the top pad 94. Adjacent to each flow aperture 136, a chamber locator aperture 138 is defined in the top pad 94. The chamber locator aperture 138 is designed for receiving a fastener (not shown) for securing the chamber element 96 to the carrier top 92.

Referring now to FIGs. 19-23, there is shown a chamber element 96. The chamber element 96 is substantially rectangular in shape having a length of approximately 2.5 inches, a width of approximately 1.0 inch, and a thickness of approximately 0.1 inches. The chamber element 96 is made from an elastomer, such as Multi-Flex TPE D 4210, or any suitable material. The surface of the chamber element can be treated by siliconizing or silanizing the surface to increase its hydrophilic properties. The chamber element 96 is disposable after each operation. The chamber element includes an inner surface 140, an outer surface 142, a first side 144, a second side 146, a first end 148, a second end 150, a first orifice 152, a second orifice 154, a first chamber locator aperture 156, a second chamber locator aperture 158, a raised portion 160, a plurality of ridges 162, and a ledge 164.

The first orifice 152 is located proximately to the first end 148 of the chamber element 96. The second orifice 154 is located proximately to the second end 150 of the chamber element 96. Illustrated in FIG. 23, there is shown a detailed view of the first orifice 152. Since the geometry of the first and second orifices 152, 154 are the substantially the same, only the first orifice 152 will be described. The first orifice 152 includes a first taper 166 wherein the diameter of the orifice is approximately 0.08 inches at the inner surface 140 and approximately 0.045 inches at a location interior to the chamber element 96. The first taper 166 has a radius of curvature of approximately 0.15 inches. The first taper 166 helps control fluid flow towards the inner surface 140. The first taper 166 is integral with a second taper 168 that is located within the chamber element 96. The second taper 168 has a radius of curvature of approximately 0.05 inches. The second taper 168 provides an interface for sealing with the needle assembly. The needle assembly will be described in more detail below. An annular portion 170 of the first orifice 152 is located adjacent to the second taper 168. The annular portion 170 has a diameter of approximately 0.065 inches. The first orifice 152 further includes a third taper 172 located adjacent to the annular portion 170. The third taper 172 is linear wherein the diameter of the third taper is approximately 0.065 at a location adjacent to the annular portion 170 and approximately 0.085 at the outer surface 142. The third taper 172 helps guide the needle assembly into the first orifice 152 such that if the needle assembly is not exactly aligned with the first orifice 152, the third taper 172 will direct the needle assembly into the first orifice 152. Although the first and second orifices 152, 154 are shown having three tapers 166, 168, 172 and a

single annular portion 170, the invention is not so limited. The first and second orifices 152, 154 serve as inlet and/or outlet ports for fluids. As seen in FIG. 23, the first orifice 152 projects outwardly from the outer surface 142 by a distance of approximately 0.03 inches.

To allow the chamber element 96 to be secured to the carrier top 92, the first and second chamber locator apertures 156, 158 are formed in the chamber element 96. The first chamber locator aperture 156 is substantially circular and is located between the first orifice 152 and the first end 148. The second chamber locator aperture 158 is slightly elongated in shape so as to form a slot and is located between the second orifice 154 and the second end 150. The first chamber locator aperture 156 serves to locate the chamber element 96 on the carrier top 92 and the second chamber locator aperture 158 provides some tolerance accommodation to allow the chamber element 96 to locate on the carrier top 92.

The chamber element 96 further includes a raised portion 160 extending from the inner surface 140. The raised portion 160 of the inner surface 140 defines an interior 174. The interior 174 is defined by the raised portion 160, and a portion of the inner surface 140 of the chamber element 96 that is encompassed by the raised portion 160. As shown in FIG. 19, the raised portion 160 is a continuous rib 176 integrally formed with the inner surface 140. Although FIG. 19 illustrates one continuous rib 176, the invention is not so limited such that at least one rib 176 may be formed and, furthermore, the raised portion need not define a rib 176.

The rib 176 is raised and projects outwardly from the inner surface 140 a distance of approximately 0.005 inches. When the chamber element 96 is positioned against an examination surface such as a standard slide 53, the rib 176 of the chamber element 96 forms a continuous chamber wall. The inner surface 140 of the chamber element 96 that is encompassed by the rib 176 forms a top of a chamber and the surface of the slide 53 that is encompassed by the rib 176 forms the bottom of the chamber. The rib 176 itself forming the side wall of the chamber.

As can be seen in FIG. 19, the rib 176 includes two opposing substantially parallel sides--a first side 178 and a second side 180. The rib 176 also includes two opposing substantially parallel ends-- a first end 182 and a second end 184. The first and second sides 178, 180 and the first and second ends 182, 184 are interconnected at curved corners

186. The first end 182 of the rib 176 is proximate to the first end 148 of the chamber element 96 and the second end 184 of the rib 176 is proximate to the second end 150 of the chamber element 96. The continuous rib 176 encompasses both the first and second orifices 152, 154 such that the first end 182 of the rib 176 encompasses the first orifice 152 and the second end 184 of the rib 176 encompasses the second orifice 154. The first end 182 of the rib 176 includes a first jog region 188 wherein the first orifice 152 is positioned so as to be seated in the first jog region 188. The second end 184 of the rib 176 includes a second jog region 190 wherein the second orifice 154 is positioned so as to be seated in the second jog region 190. The first and second orifices 152, 154 may be partially seated in the first and second jog regions 188, 190, respectively.

Still referencing FIG. 19, four ridges 162 are formed on the inner surface 140 of the chamber element 96 and are integrally formed therewith. Two of the ridges 162 are located between the first end 182 of the rib 176 and the first end 148 of the chamber element 96 and two of the ridges 162 are located between the second end 184 of the rib 176 and the second end 150 of the chamber element 96. However, any number of ridges 162 may be employed. The ridges 162 serve as stops to limit the downward travel of the chamber element 96 when force is applied to sealingly engage the rib 172 to the slide 53.

A ledge 164 is defined adjacent to the first end 148 of the chamber element 96. The ledge 164 is a recessed portion of the chamber element 96. The ledge 164 is designed to clear a bar code label (not shown) that is usually placed on the end of the slide 53.

To assemble the carrier top assembly 30, first, the carrier clamp assembly 32 is placed in the recess 110 of the carrier top 92. Fasteners are used to secure the carrier clamp assembly 32 and the carrier top 92.

Referring now to FIGs. 24 and 25, there is shown a carrier clamp assembly 32. The carrier clamp assembly 32 includes a block 194, a first hook assembly 196, and a second hook assembly 198. The block 194 is dimensioned such that it fits into the recess 110 of the carrier top 92. The block 194 includes fastener features 113, a first pair of bores 200 for securing the first hook assembly 196 to the block 194 and a second pair of bores 202 for securing the second hook assembly 198. The block 194 is secured to the carrier top 92 via fastener features 113 in block 194 and fastener features 111 in the carrier top. Because the construction of the first hook assembly 196 is substantially the same as the second hook assembly 198 only the first hook assembly 196 will be described.

As shown in FIG. 25, the first hook assembly 196 includes a base element 204, a linkage 206, a pivot 208, a hook 210, and a lever 212. The base element 204 is inserted into the block 194 and secured thereto with fasteners 214 passed through the first pair of bores 200. The base element 204 is rotatably coupled to the linkage 206 and the lever 212 is connected to the linkage 206. The pivot 208 is pivotally coupled to the linkage 206 and the hook 210 is connected to the pivot 208.

The top pad 94 is placed on the carrier top 92 and into the pad recess 130 such that the pad locator apertures 134 of the top pad 94 are aligned with the pad locator bores 122 of the carrier top 92. Fasteners 192 are passed through the pad locator apertures 134 and into the pad locator bores 122 to secure the top pad 94 to the carrier top 92. After the top pad 94 is secured to the carrier top 92, the flow apertures 136 of the top pad 94 and the flow apertures 116 of the carrier top 92 will be in alignment, and the chamber locator bores pins and the chamber locator apertures 138 of the top pad 94 will be in alignment. Then, the chamber elements 96 are pressed onto the pins. Female members 128 are inserted into the female-member bores 126 of the carrier top 92.

An assembled carrier 22 assembly is shown in FIGs. 4 and 5. Assembly of the carrier assembly 22 will now be discussed. Slides 53 are inserted into the slide apertures 86 of the slide locator 38. The carrier assembly 30 and the carrier base assembly 28 are joined such that the male members 58 of the carrier base 28 are mated with the female members 128 of the carrier top assembly 30.

Once the carrier top assembly 30 and carrier base assembly 28 are joined, the hooks 210 of the first and second hook assemblies 196, 198 are latched over the latch pins 70 of the carrier base assembly 28 and then the levers 212 are rotated to join the carrier top assembly 30 and the carrier base assembly 28 together. With the carrier top assembly 30 and the carrier base assembly 28 joined together, the raised portion 160 of the chamber element 96 engages the examination surface or slide 53 such that a chamber is formed. A seal is formed between the chamber element 96 and the slide 53 as a result of the pressure applied on the slide 53 by the chamber element 96 such that liquid may not escape across the interface between the chamber element 96 and slide 53. Although a pressure seal is disclosed, a seal employing adhesive may also be employed.

The chamber that is formed is defined by the raised portion 160, the inner surface 140 of the chamber element 96 that is encompassed by the raised portion 160, and the

surface area of the slide 53 that is encompassed by the raised portion 160. The raised portion 160 or rib 176 forms the side wall of the chamber. The inner surface 140 of the chamber element that is encompassed by the raised portion 160 forms a top of the chamber. The surface area of the slide 53 that is encompassed by the rib 176 or raised portion 160 forms a base of the chamber. The ridges 162 of the chamber element 96 may also engage the examination surface or slide 53 to serve as a stop to prevent further travel of the chamber element 96 towards the slide 53 so as to prevent collapse of the chamber. The inner surface 140 of the chamber element 96 that is encompassed by rib 176 or raised portion 160 is spaced from the slide surface by a distance of approximately 0.0034 inches and the resulting chamber volume is approximately 125 µl.

The wash station assembly 12 with the carrier assembly 22 removed is depicted in FIG. 26. After the carrier assembly 22 is assembled, it is ready to be inserted into the wash station assembly 12.

The needle assembly 24 is shown in FIG. 27. The needle assembly 24 includes a needle frame 216, a plurality of needle systems 218, and at least one cover plate 220.

Referring now to FIG. 28, there is shown a needle frame 216. The needle frame 216 includes at least one horizontal travel slide (not shown), a plurality of needle apertures 224, needle cover supports 226, and a plurality of needle cover apertures 228. The horizontal travel slide 222 is mounted to the frame structure 26 so as to permit horizontal movement of the needle frame 216.

Referring now to FIGs. 27-33, each of the needle systems 218 depicted in FIG. 27 includes a guide pin 230, a guide pin spring 231, a wash needle spring 232, and a needle tube 234. As shown in FIG. 29, the needle tube 234 is substantially cylindrical in shape and includes a first end 236 that is tapered and a second end 238. A fluid passage 240 is defined within the needle tube 234. The needle tube 234 also includes a tube stop 242. As shown in FIGs. 30 and 31, the guide pin 230 is generally cylindrical having a passage 244 dimensioned for receiving the needle tube 234. The guide pin 230 includes a first end 246, a second end 248, a first portion 250, and a second portion 252. The first portion 250 has a diameter that is smaller relative to the diameter of the second portion 252 of the guide pin 230. The first end 246 is tapered and a recess 254 dimensioned for receiving the guide pin spring 231.

Each of the needle systems 218 is assembled by inserting the needle tube 234 into the passage 244 of the guide pin 230 such that the needle tube stop 242 abuts the recess 254 of the guide pin 230. The needle systems 218 are then inserted into the needle apertures 224 of the needle frame 216. The wash needle spring 232 is then added over the needle tube 234 and abuts the needle tube stop 242. The guide pin spring 231 is then generally placed around the needle tube 234. The cover plate 220 is substantially a rectangular plate having a plurality of needle apertures 256 and at least one cover plate aperture 258. The cover plate 220 is placed over the needle systems 218 such that the needle tubes 234 pass through the needle apertures 256 in the cover plate 220. The cover plate 220 is attached to the needle frame 216 with fasteners. Although two cover plates 220 are shown in FIG. 27, the invention is not so limited.

The frame structure 26 is seen in FIGs. 3 and 34. The frame structure 26 includes a horizontal travel rail 260, a vertical travel rail 262, a base frame 264, a handle 266, and a shield 268. The shield 268 and handle 266 are connected to the horizontal travel rail 260. The horizontal travel rail 260 is connected to the vertical travel rail 262 which is connected to the base frame 264. The base frame 264 includes a heating/cooling platform 270, a carrier assembly platform 272, a wash tip drain 274, a carrier assembly lock 276, and a wash assembly lock 278.

The needle frame 216 is mounted to the frame structure 26 such that the horizontal travel slide (not shown) of the needle frame 216 engages the horizontal travel rail 260 such that the needle frame 216 can be moved horizontally along the horizontal travel rail 260. Rail 260 attached to the vertical travel rail 262 allows vertical travel of assembly.

The carrier assembly 22 is located on the carrier assembly platform 272 and may be locked in position with the carrier assembly lock 276. This position has the carrier assembly 22 down and in contact with the heating/cooling platform 270. The needle assembly 24 is moved along the horizontal rail 260 to a position wherein the guide pins 230 of the needle assembly 24 are substantially aligned with the flow apertures 116 of the carrier top 92. The needle assembly 24 is then moved vertically down towards the carrier assembly 22. As the needle assembly 22 is lowered, the guide pins 230 contact the carrier top 92. The guides pins 230 direct the position of the needle tubes 234 relative to the carrier top 92. The tapered first end 246 of the guide pin 230 together with the tapered end 118 of the flow aperture 116 of the carrier top 92 guide the needle tube 234. As the needle

assembly continues towards the carrier assembly 22, the needle tubes 234 enter the orifices 152, 154 of the chamber elements 96 and the needle tubes 234 seal against the orifices 152, 154 of the chamber elements 96. When positioned, the wash station assembly 12 is locked into position with the wash assembly lock 278. When the wash assembly lock 278 is disengaged and the needle assembly 24 is moved upwards along the vertical rail 262 and then horizontally along the horizontal rail 260. The needle tubes 234 are free to drip fluid into the wash tip drain 274. If the carrier assembly lock 276 is disengaged, the carrier assembly 22 may be removed from the wash station if desired.

Referring now to FIGs. 1 and 35, there is shown one variation of a fluid delivery system 14 that can be employed with the wash station assembly 12 of the present invention. The fluid delivery system 14 delivers various fluids such as a wash fluid and a sample containing fluid, to and from the carrier assembly 22. A schematic of the fluid delivery system 14 is shown in FIG. 35. The fluid delivery system 14 includes a plurality of fluid reservoirs 280, at least one pump 282 for moving fluid, a valve system 284, needle system 218, a waste manifold 286, and a waste reservoir 288.

As shown in FIG. 35, the fluid reservoirs 280 or fluid sources are fluidly connected to a valve system 284. The valve system includes one or more valves 292 and a manifold 290 for directing one or more different fluids to the chamber. The valve system 284 may be coupled to a controller and the valves 292 may be adjusted manually or automatically. The valve system 284 allows for selectively connecting one or more fluid reservoirs 280. For example, for washing, a selected valve 292 may be opened to provide a fluid connection. Although multiple independent valves 292 in combination with a manifold are illustrated in FIG. 35, multi-port distribution valves may be employed. Fluid from the fluid reservoirs 280 passes via tubing into a manifold 290. From the manifold 290, fluid is directed to a first set of pumps 296 and to a second set of pumps 298. Each of the first and second set of pumps 282 is shown to have six pumps 282; however, the invention is not so limited and any number of pumps 282 may be employed. Fluid from the first set of pumps 296 is directed via tubing 294 to the needle assembly 24 of the first wash station assembly 12. Fluid from the second set of pumps 298 is directed via tubing to the needle assembly 24 of the second wash station assembly 12. Although syringe pumps, such as the Cavro model XP 3000 syringe pump, are illustrated in FIG. 35, a number of different pump types,

such as peristaltic pumps and diaphragm pumps, may be used to deliver fluids to the chamber.

Generally, fluid from the needle assembly 24 enters each chamber via the first orifice 152 and exits the chamber via the second orifice 154. Fluid from the chamber enters a waste manifold 286 via tubing and is directed towards a waste reservoir 288 via a first waste pump 300. Although a diaphragm pump is illustrated, a number of different pump types may be employed.

Still referencing FIGs. 1 and 35, a sample delivery system 16 includes a microwell plate 302, a sample pump 304, a sample tip 306, a sample tip wash station 308, and an automated arm 310. Sample to be delivered to the chamber is located in each microwell 312 of the microwell plate 302 that serves as a fluid source.

Sample from the microwell plate 302 is drawn by the sample tip 306. The sample tip 306 is in fluid communication with the sample pump 304. As shown in FIG. 35, a syringe pump is used, however, any suitable pump may be employed. The sample pump 304 may be fluidly connected to one or more fluid reservoirs 280 via a valve 314. The sample tip 306 is automatically directed to and from the microwell plate 302 as well as to and from the sample tip wash station 308 by the automated arm 310. The automated arm 310 is controlled by a controller (not shown) such as a process controller 20 to draw sample from appropriate microwells 312 and deliver sample to one or more chambers. The automated arm 310 is automated to move the sample tip 306 vertically and horizontally as directed by the controller. Also provided is a sample tip wash station 308 wherein the sample tip 306 can be substantially flushed clean. The sample tip wash station 308 is fluidly connected to a waste reservoir 288 via a pump 316.

The hybridization station 10 includes a temperature control system 18. The temperature control system 18 operates to maintain the temperature within the hybridization chamber 10 at optimized levels according to a preselected temperature profile. The temperature control system 18 generally monitors and controls the temperature of the various fluids delivered to the chamber.

For example, the temperature of sample in the microwell plate 302 is controlled by the temperature control system 18. A desired temperature is maintained within the microwell plate 302 by thermal exchange across the microwell plate 302 and a temperature control block 318 against which the microwell plate 302 is placed as shown in FIG. 35.

Adjacent to the temperature control block 318 is at least one Peltier heater/cooler 320 and a fan-cooled heat sink 322. These Peltier heater/coolers 320 are in thermal communication with the sample in the microwell plate 302.

Also, the temperature of the chamber is maintained at a desired temperature by the temperature control system 18 via a heating/cooling assembly 324 that is located on the heating/cooling assembly platform 270 adjacent to the carrier assembly 22. The heating/cooling assembly 324 includes a temperature control block 326, a Peltier heater/cooler 328, and a heat sink 330, as shown in FIGs. 2, 3, and 26. A desired temperature is maintained within the chamber by thermal exchange across the carrier assembly 22 and the temperature control block 326. The Peltier heater/cooler 328 is shown to be adjacent to a fan-cooled heat sink 330 and is in thermal communication with the chamber.

The fluid delivery system 14 also includes temperature control elements 322 controlled by the temperature control system 18 for maintaining a desired temperature of the fluids delivered to the chamber of the carrier assembly 22. The temperature of the fluid can be controlled in different ways. For example, as shown in FIG. 35, temperature control elements 322, such as fluid heaters, are located adjacent to tubing at a location just prior to the carrier assembly 22. Any number of fluid heaters/coolers, controlled by the temperature control system 18, may be employed along and in thermal communication with the fluid path to maintain the desired fluid temperature. Furthermore, at least one precision temperature sensor (not shown) is embedded close to the chamber or other locations to provide accurate temperature control.

The hybridization station 10 also includes a process controller 20 for automatically carrying out the various steps involved in hybridization. The process controller 20 generally controls and monitors the hybridization station 10 including the fluid delivery system 14, the sample delivery system 16, and the temperature control system 18 according to a preprogrammed set of instructions. This generally involves delivering sample and/or wash fluids to the hybridization chamber at selected times during a hybridization operation and controlling the temperature of the hybridization chamber according to a selected temperature profile.

Process control is generally carried out by an onboard processor contained within the hybridization station 10 itself. The onboard processor is typically appropriately

programmed to operate the above described systems according to an input set of process parameters. Specifically, the processor operates to provide appropriate instructions to each of the elements of the hybridization station 10 according to a pre-selected time/temperature/mixing profile/flow rate selected by the user including pump or valve operation, temperature control system operation, etc. Alternatively, the process parameters may be input by the user into a computer that is connected to the hybridization station. Custom software controls allow modifications of the mixing protocol.

The hybridization station is operated to deliver reagents, samples, buffer and wash solutions to the hybridization chamber, and to maintain optimal reaction conditions, e.g., temperature and mixing, within the hybridization chamber for a preselected time or number of cycles. Operation of the hybridization chamber begins with the insertion of at least one micro-arrayed slide into the slide locator 38 of the carrier base assembly 28. The carrier top assembly 30 and carrier base assembly 28 are joined, as previously described, and the carrier assembly 22 is positioned atop the carrier assembly platform 272. Positioning the carrier assembly 22 onto the carrier platform 272 automatically aligns the carrier assembly 22 for subsequent operations by virtue of the inclusion of alignment structures on the frame structure 26 as well as the carrier assembly 22.

With the carrier assembly 22 secured in the frame structure 26, a solution containing a target nucleic acid is automatically delivered from the microwell plate 302 to the hybridization chambers with the sample tip 306 being directed by the automated arm 310 controlled by the process controller 20. Typically, the solution containing target nucleic acid incorporates a fluorescent label for subsequent detection.

The process controller 20 can be pre-programmed to follow any number of wash protocols. If, for example, the first solution to be delivered to the chamber after hybridization is a buffer solution, the needle assembly 24 is lowered along the vertical rail 262 until the needle systems 218 engage the chamber element 96 and pumps 282 deliver the initial solution to the hybridization chamber via the first set of orifices 152 of the chamber elements 96. The rate at which fluid is pumped into and out of the chamber is controlled to avoid the formation of air bubbles within the chamber. The rate at which fluid is pumped into the chamber is approximately 25µl/second. This rate can vary between approximately 6µl/second to approximately 100 µl/second. The rate at which

fluid is pumped from the chamber can vary between 6μl/second to approximately 100 μl/second. The chamber is filled for a set time period.

The carrier assemblies 22 may be removed from the hybridization station 10 to be placed in a humidity controlled incubator at a temperature of approximately 40° C. Alternatively, the carrier assemblies may remain in the hybridization station 10 while the chambers are incubated on the hybridization station 10, or the entire station 10 could be incubated. Once the carrier assemblies 22 are removed from the hybridization station 10, the hybridization station is free for inserting additional carrier assemblies 23. This method of removing at least one carrier assembly 22 from the hybridization station 10 and then inserting at least one other carrier assembly 22 greatly expedites the hybridization process and is made possible by the removable carrier assembly 22. Although the station 10 is referred to as a hybridization station 10, it is not so limited, that is, actual hybridization does not necessarily have to take place within the station 10. For this reason, the hybridization station 10 of the instant invention may be interchangeably and equally appropriately called a fluidics station. Whether the station 10 is called a hybridization station 10 or a fluidics station is not limiting with respect to whether hybridization actually takes place within the station 10.

Once removed from the hybridization station 10, the carrier assembly 22 is maintained at an appropriate temperature and time period for the particular hybridization reaction. Appropriate time periods can vary widely depending on the hybridization protocol and are generally long periods of time typically in excess of twelve hours. Appropriate temperatures are generally in the range of acceptable biological temperatures such as approximately 30° C to approximately 40° C, but will often vary from this range, depending upon the reaction being performed, or the nature of the species involved in the hybridization.

Although static hybridization reactions may be performed in the hybridization chamber, it is sometimes preferred to provide agitation or mixing within the hybridization chamber to ensure contact between target molecules and probes on the array. The consequences of inadequate mixing include slower binding rates of the target to the array and possibly lower overall fluorescence signals if the hybridization reaction does not reach equilibrium by the end of the incubation period. Accordingly, mixing can be provided in a variety of ways including mechanical mixing, rocking mixing, and push-pull mixing. For

example, a "drain and fill" operation can also be performed. This operation involves repeated draining and filling of the hybridization chamber with the sample. In operation, once the chamber is initially filled, the "drain and fill" operation involves the reversal of the pump which draws the sample out of the hybridization chamber. During this operation, the sample is either being returned to its reservoir or is retained in the volume of the tubing. Thus, little or no sample volume is lost during this operation. Mixing can also be provided by push and pull mixing wherein the chamber is pushed in a horizontal direction and then pulled back in the opposite but horizontal direction.

Following hybridization for a preselected time period, the carrier assembly 22 is returned to the hybridization station 10 for a wash process. The needle assembly 24 is lowered such that the needle systems 218 engage and seal against the chamber element. In the wash process, the hybridization station 10 will typically deliver a wash solution, and/or buffer to the hybridization chamber, to rinse substantially all of the solution containing sample from the chamber. Pumps 282 are activated and wash and/or buffer is delivered from the appropriate valved reservoirs 280 into the hybridization chamber via first orifices 152 in the chamber element and out of the hybridization chamber via the second set of apertures in the chamber elements 96 for example. Washing the hybridization chamber avoids any difficulty associated with background fluorescence that can impede clear and accurate determinations of hybridization. Wash steps will typically be repeated as desired, to sufficiently reduce or eliminate any remaining, unhybridized target. Typically, the wash steps will be repeated from two to ten times.

Following washing, the carrier assembly 22 is removed from the hybridization station 10 and opened by removing the carrier top. The slides 53 are also removed. The slides 53 may be dipped in a final water bath, dried and transferred to a reader/scanner device to identify the locations on the array to which the target hybridized.

The hybridization station 10 can be utilized to load sample-containing solution into the chambers, incubate the slide arrays, perform limited mixing if necessary, and wash the slide arrays without removal of the carrier assembly from the hybridization station 10. In one variation, the hybridization station 10 can be utilized to load sample-containing solution into the chambers and perform all of the functions except incubation in the hybridization station 10 wherein the carrier assembly would be removed from the hybridization station 10 for the incubation process. After incubation, the carrier assembly

22 would be returned to the hybridization station 10 for washing the slides 53. Significant cost savings and greater throughput can be realized with the above variation in comparison with prior art devices.

While the present invention has been described with reference to one or more particular variations, those skilled in the art will recognize that many changes may be made thereto without departing from the spirit and scope of the present invention. Each of these embodiments and obvious variations thereof are contemplated as falling within the spirit and scope of the claimed invention, which is set forth in the following claims.

CLAIMS

What is claimed is:

1. A chamber comprising:

an examination surface;

a chamber element having an inner surface and a raised portion defining an interior, the raised portion extending from the inner surface;

the chamber being formed by the chamber element contacting the examination surface such that the raised portion engages the examination surface, the chamber being defined by the examination surface and the interior; the inner surface of the interior being spaced from the examination surface.

2. The chamber of claim 1 wherein the raised portion is at least one rib.

3. The chamber of claim 2 wherein the at least one rib is continuous.

4. The chamber of claim 1 wherein the raised portion is integrally formed with the chamber element.

5. The chamber of claim 1 wherein the raised portion is continuous.

6. The chamber of claim 1 wherein the examination surface is a slide.

7. The chamber of claim 1 wherein the raised portion is at least approximately 0.002 inches in height when relaxed.

8. The chamber of claim 1 wherein the raised portion is at least approximately 0.002 inches when pressed against the examination surface.

9. The chamber of claim 1 wherein the raised portion is adapted to sealingly engage the examination surface.

10. The chamber of claim 1 wherein chamber element further includes an outer surface and a first orifice extending between the outer surface and the inner surface, the raised portion encompassing the first orifice.

11. The chamber of claim 10 wherein the first orifice includes a first taper, the first taper opening to the inner surface.

12. The chamber of claim 10 wherein the first orifice is adapted to receive a needle tube at the outer surface, the first orifice and the needle tube being adapted to engage to form a sealing interface.

13. The chamber of claim 1 wherein the interior is substantially rectangular in shape.

14. The chamber of claim 10 wherein the interior includes a first end and a second end, the first orifice being located at the first end adjacent to the raised portion.

15. The chamber of claim 14 wherein the raised portion includes a first jog region, the first orifice being substantially seated in the first jog region.

16. The chamber of claim 15 wherein the first jog region is substantially centrally located along the first end.

17. The chamber of claim 14 wherein the chamber element further includes a second orifice extending between the outer surface and the inner surface, the raised portion encompassing the second orifice.

18. The chamber of claim 17 wherein the second orifice includes a first taper, the first taper opening to the inner surface.

19. The chamber of claim 17 wherein the second orifice is adapted to receive a needle tube at the outer surface, the second orifice and the needle tube being adapted to engage to form a sealing interface.

20. The chamber of claim 17 wherein the second orifice is located at the second end adjacent to the raised portion.

21. The chamber of claim 20 wherein the raised portion includes a second jog region, the second orifice being substantially seated in the second jog region.

22. The chamber of claim 21 wherein the second jog region is substantially centrally located along the second end.

23. The chamber of claim 1 wherein the chamber element includes at least one aperture for receiving at least one fastener.

24. The chamber of claim 1 wherein the chamber element includes at least one ridge extending from the inner surface, the ridge being adapted to prevent the raised portion from collapsing under pressure.

25. The chamber of claim 1 further including a carrier top, the chamber element being connected to a carrier top.

26. The chamber of claim 25 further including a top pad located between the chamber element and the carrier top.

27. The chamber of claim 25 further including a carrier bottom, the examination surface being located the carrier bottom.

28. The chamber of claim 27 wherein the carrier top and carrier bottom are joined to engage the chamber element and the examination surface.

29. The chamber of claim 28 further including a clamp, the carrier top and carrier bottom being joined by the clamp.

30. A carrier comprising:

at least one chamber, the chamber being formed by a chamber element contacting an examination surface, the chamber element having an inner surface and a raised portion extending from the inner surface, the inner surface of the chamber element that is encompassed by the raised portion being spaced from the examination surface by the raised portion.

31. The carrier of claim 30 wherein the examination surface is a slide.

32. The carrier of claim 30 wherein the inner surface of the chamber element that is encompassed by the raised portion is spaced from the examination surface by a distance of approximately 0.002 inches.

33. The carrier of claim 30 wherein the chamber element includes at least one orifice.

34. The carrier of claim 33 wherein the carrier is removably insertable into a wash station assembly.

35. The carrier of claim 34 wherein the wash station assembly includes a needle assembly, the needle assembly being adapted to engage the carrier such that the at least one chamber of the carrier is in fluid communication with at least one fluid source.

36. The carrier of claim 35 wherein the needle assembly includes at least one needle system, the needle system including a guide pin and a needle tube, the guide pin having a passage for receiving the needle tube, the needle tube being inserted into the passage of the guide pin, the needle tube having a fluid passage.

37. The carrier of claim 36 wherein the needle assembly further includes a frame, a cover plate connected to the frame, and a spring, the guide pin being located in the frame, the needle tube being located in the guide pin, the spring being disposed around the needle tube and between the guide pin and the cover plate such that when the guide pin engages the carrier the needle tube projects outwardly from the guide pin to engage the chamber element.

38. The carrier of claim 37 further including a locator spring disposed between the cover plate and guide pin.

39. A method comprising:

providing a station having a carrier, a wash station, the carrier being removably insertable into the wash station;

loading at least one slide having sample coupled to an examination surface into the carrier;

providing a chamber element, the chamber element being disposed in the carrier, the chamber element having an inner surface and a raised portion extending from the inner surface, the chamber element having at least one orifice;

locating at least one chamber element over the at least one slide to form a chamber such that the raised portion contacts the slide and the inner surface that is encompassed by the raised portion is spaced from the examination surface, the raised portion contacting the slide such that fluid does not cross the raised portion;

loading the carrier into the wash station; and

injecting fluid into the chamber through the at least one orifice.

40. The method of claim 39 wherein the step of injecting fluid into the chamber includes providing at least one needle tube and at least one fluid source; the at least one needle tube being in fluid communication with the at least one fluid source.

41. The method of claim 40 wherein the step of injecting fluid into the chamber includes the step of injecting fluid through via the at least one needle tube, the at least one needle tube being in fluid communication with at least one fluid source, the at least one fluid source being at least one microwell plate.

42. The method of claim 40 wherein the step of injecting fluid further includes providing an automated arm for directing the at least one needle tube.

43. The method of claim 40 wherein the step of providing at least one needle tube and at least one fluid source includes providing a guide pin, a spring, a frame, and cover plate connected to the frame, the needle tube being disposed in the guide pin, the guide pin being located in the frame, the spring being disposed around the needle tube and between the guide pin and cover plate such that when the guide pin engages the carrier the needle tube projects outwardly from the guide pin to engage the chamber element.

44. The method of claim 43 further including the step of removing fluid from the chamber through via the at least one orifice.

45. The method of claim 39 further including the step of controlling the temperature of the fluid.

46. The method of claim 45 wherein the step of controlling the temperature of the fluid includes providing at least one heating/cooling element.

47. The method of claim 46 wherein the step of providing at least one heating/cooling element includes providing at least one heating/cooling element in thermal communication with the fluid.

48. A method comprising:

inserting at least one first carrier into a station, the at least one first carrier having at least one chamber;

injecting a solution into the at least one chamber of the first carrier;

removing the at least one first carrier from the station to free the station for receiving at least one second carrier, the at least one second carrier having at least one chamber; and

inserting the at least one second carrier into the station.

49. The method of claim 48 wherein the solution contains assayed nucleic acid.

50. The method of claim 48 wherein the solution is a wash solution.

51. The method of claim 48 further including the step of removing solution from the at least one chamber of the first carrier.

52. The method of claim 48 further including the step injecting the at least one chamber of the second carrier with solution.

53. The method of claim 52 further including the step of removing solution from the at least one chamber of the second carrier.

54. A carrier removably insertable into a station comprising:

at least one chamber, the chamber having a first surface and a second surface, the second surface having a side wall extending from the second surface, the side wall of the second surface contacting the first surface and encompassing sample coupled to the first surface, a portion of the second surface that is encompassed by the side wall being spaced from the first surface.

55. The carrier of claim 54 wherein the first surface is a slide

56. The carrier of claim 54 wherein the second surface is at least one material selected from the group consisting of: metal, plastic, ceramic, or composites thereof.

57. The carrier of claim 54 wherein the second surface includes a hydrophilic surface treatment.

58. The carrier of claim 54 wherein the second surface further includes at least one orifice.

59. The carrier of claim 58 wherein the at least one orifice is adapted to engage at least one flow tube for the delivery of fluid.

60. The carrier of claim 54 further including a carrier top and a carrier bottom, the first surface being disposed in the carrier bottom, the second surface being disposed in the carrier top.

61. The carrier of claim 54 wherein the side wall is a raised portion extending from the second surface.

62. The carrier of claim 54 wherein the side wall is integral with the second surface.

63. The carrier of claim 54 wherein the side wall is continuous.

64. The carrier of claim 54 wherein the side wall is a rib.

65. The carrier of claim 54 wherein the second surface further includes at least one raised stop.

66. The carrier of claim 54 wherein the sidewall is at least approximately 0.002 inches in height.

67. The carrier of claim 54 wherein the at least one chamber has a volume of at least approximately 0.03 cm^3.

68. A hybridization station comprising:

at least one wash station assembly;

a fluid delivery system coupled to the wash station assembly;

a sample delivery system adapted for fluid communication with the wash station assembly;

a temperature control system in thermal communication with the wash station assembly; and

a controller coupled to the fluid delivery system

69. The hybridization station of claim 68 wherein the wash station assembly includes:

a frame structure;

a carrier removably insertable into the frame structure; and

a needle assembly coupled to the frame structure.

70. The hybridization station of claim 69 wherein the carrier includes:

a carrier top; and

a carrier base joined to the carrier top.

71. The hybridization station of claim 70 wherein the carrier top and the carrier base are joined by a clamp.

72. The hybridization station of claim 70 wherein the carrier base includes a slide locator connected to the carrier base.

73. The hybridization station of claim 72 wherein the carrier base further includes a lower pad located between the slide locator and the carrier base.

74. The hybridization station of claim 72 wherein the slide locator includes a plurality of slide apertures each adapted to receive a slide.

75. The hybridization station of claim 70 wherein the carrier top includes:

at least one aperture; and

at least one chamber element connected to the carrier top.

76. The hybridization station of claim 75 wherein the carrier top assembly further includes a top pad located between the chamber element and the carrier top.

77. The hybridization station of claim 75 wherein the chamber element includes:

an outer surface; and

an inner surface, the inner surface having a raised portion extending from the inner surface.

78. The hybridization station of claim 77 wherein the chamber element includes at least one orifice extending from the inner surface to the outer surface, the at least one orifice being encompassed by the raised portion.

79. The hybridization station of claim 78 wherein the at least one orifice includes a first taper, the first taper opening to the inner surface.

80. The hybridization station of claim 77 wherein the raised portion is a rib.

81. The hybridization station of claim 77 wherein the raised portion is adapted to engage a slide located in the slide locator of the carrier base when the carrier top and the carrier base are joined.

82. The hybridization station of claim 78 wherein the raised portion includes a jog region wherein the orifice is seated within the jog region.

83. The hybridization station of claim 78 wherein the raised portion includes a jog region wherein the orifice is seated partially within the jog region.

84. The hybridization station of claim 77 wherein the inner surface includes at least one stop.

85. The hybridization station of claim 69 wherein the needle assembly includes:

a needle frame; and

a plurality of needle systems for delivering fluid; the needle systems being located in the needle frame.

86. The hybridization station of claim 85 wherein each of the needle systems includes:

a needle tube having a fluid passage; and

a guide pin dimensioned for receiving the needle tube.

87. The hybridization station of claim 86 wherein the needle assembly further includes:

a cover plate connected to the needle frame; and

a spring located between the cover plate and the guide pin, the spring encompassing needle tube.

88. The hybridization station of claim 68 wherein the fluid delivery system includes:

at least one fluid reservoir;

at least one pump connected to the fluid reservoir; and

at least one valve connected to the fluid reservoir.

89. The hybridization station of claim 68 wherein the sample delivery system includes:

a sample source;

a pump; and

a sample tip in fluid communication with the pump.

90. The hybridization station of claim 68 wherein the temperature control system includes at least one heater/cooler in thermal communication with the wash station assembly.

91. The hybridization station of claim 89 wherein the sample source is a well plate.

92. The hybridization station of claim 89 wherein the sample source is a micro-centrifuge tube.

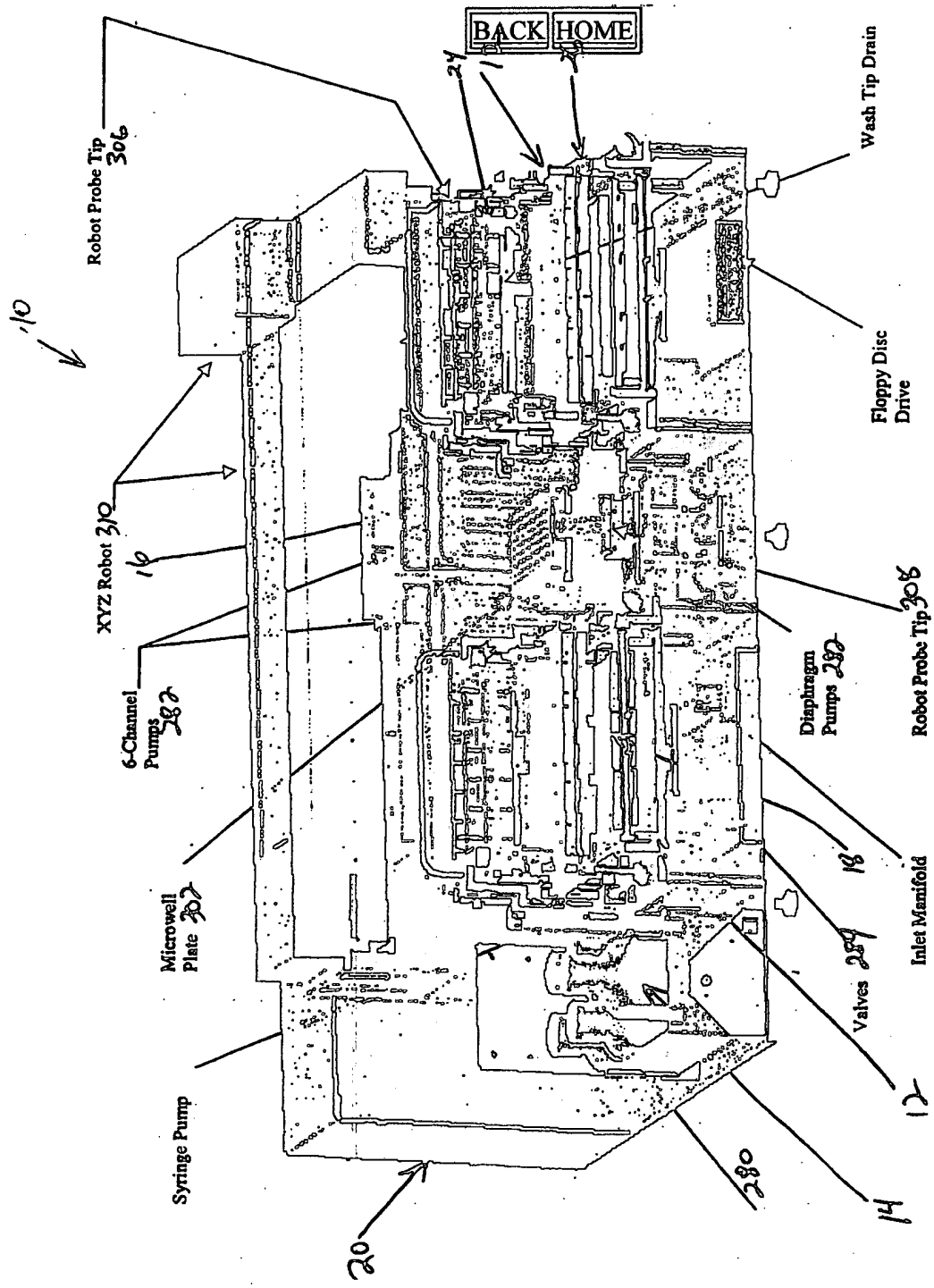
BACK HOME
Robot Probe Tip 306
Wash Tip Drain
Floppy Disc Drive
XYZ Robot 310
6-Channel Pumps 282
Diaphragm Pumps 282
Robot Probe Tip 306
Wash Station
Microwell Plate 302
Inlet Manifold
Valves 284
Syringe Pump
10
12
14
16
18
20
24
280

FIG. 1

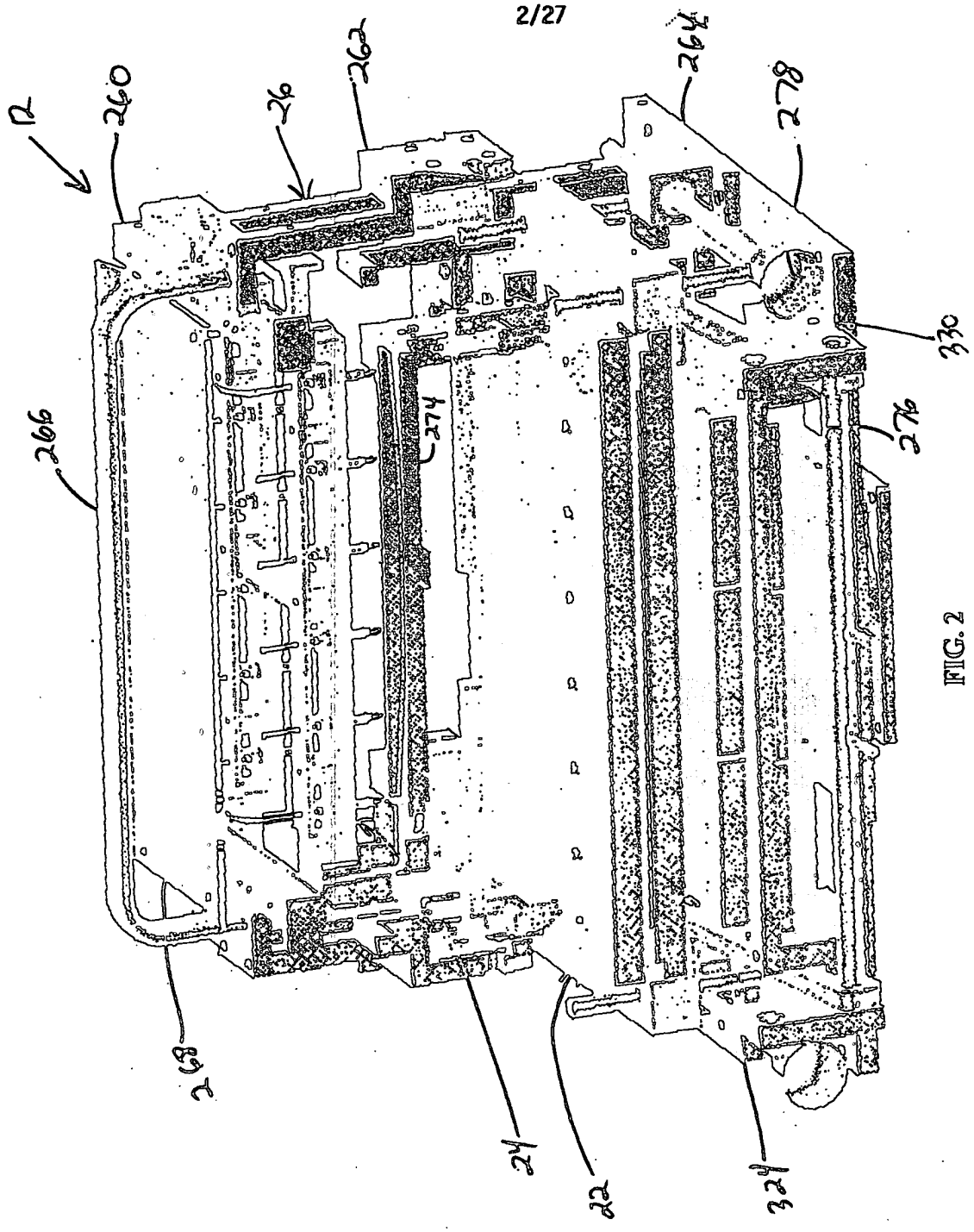

FIG. 2

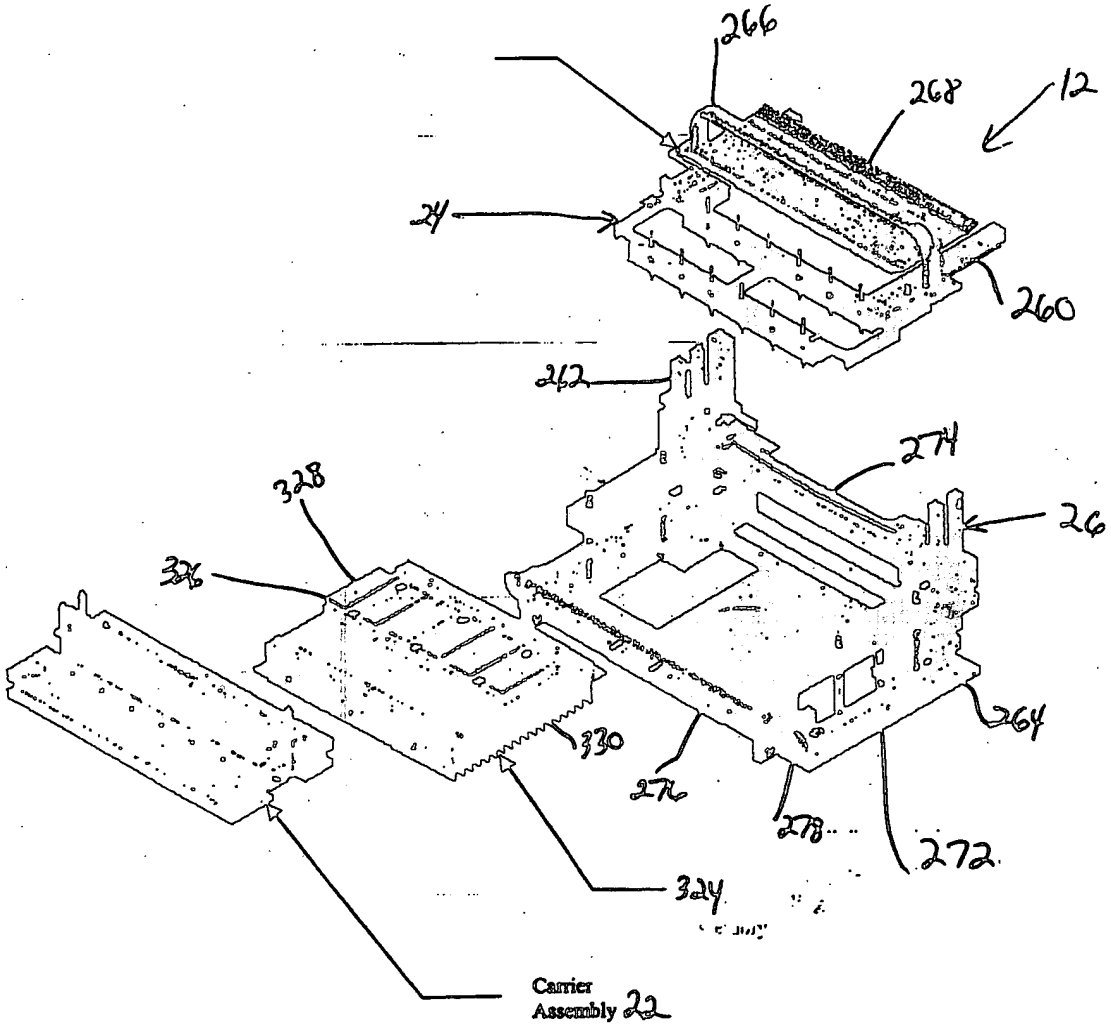
266
268
12
24
260
262
274
328
326
26
330
264
276
278
272
324
Carrier
Assembly 22

FIG. 3

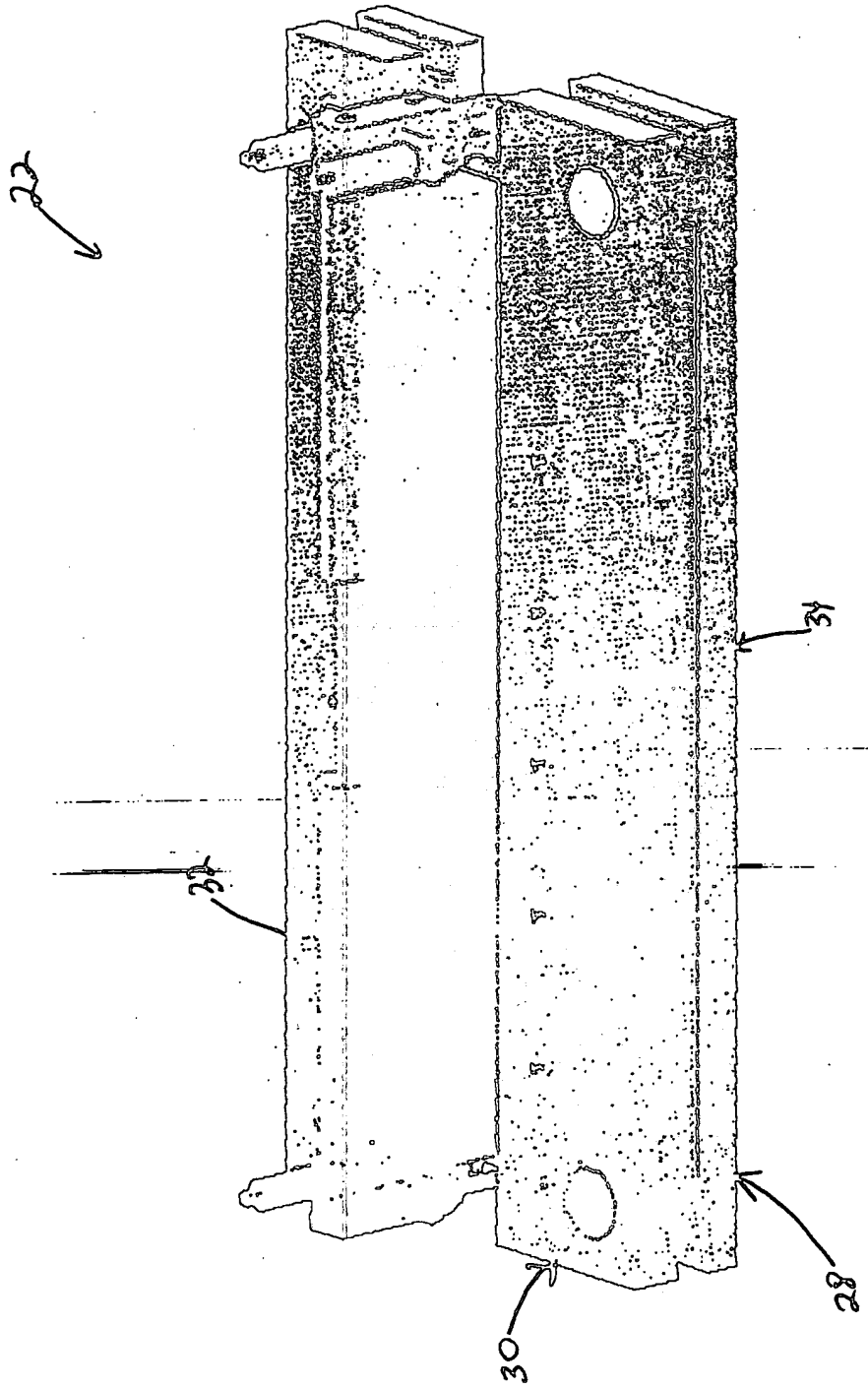

FIG. 4

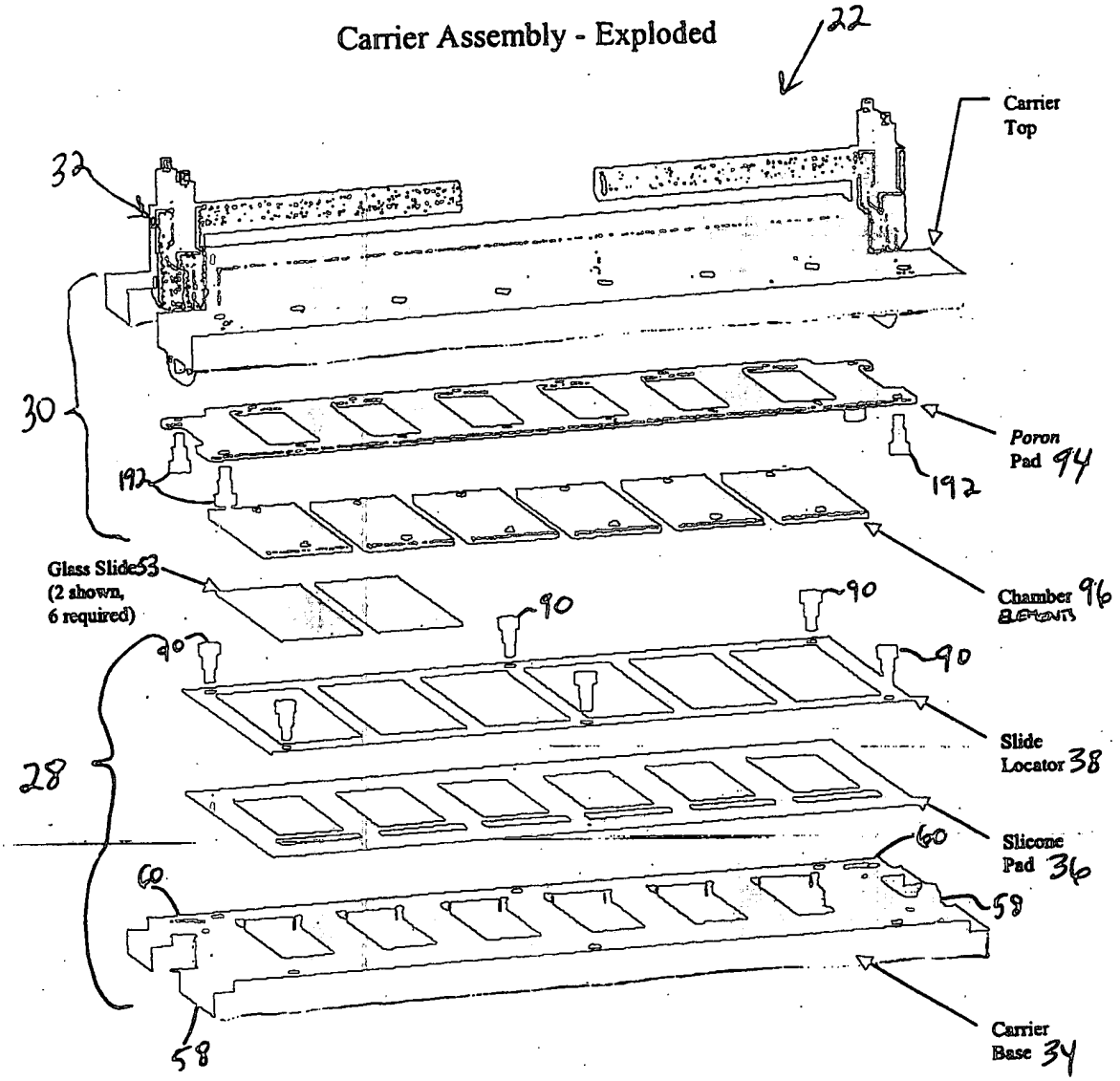
Carrier Assembly - Exploded
22
Carrier Top
32
30
Poron Pad 94
192
192
Glass Slide 53 (2 shown, 6 required)
Chamber 96 ELEMENTS
90
90
90
90
28
Slide Locator 38
Silicone Pad 36
60
60
58
58
Carrier Base 34

FIG. 5

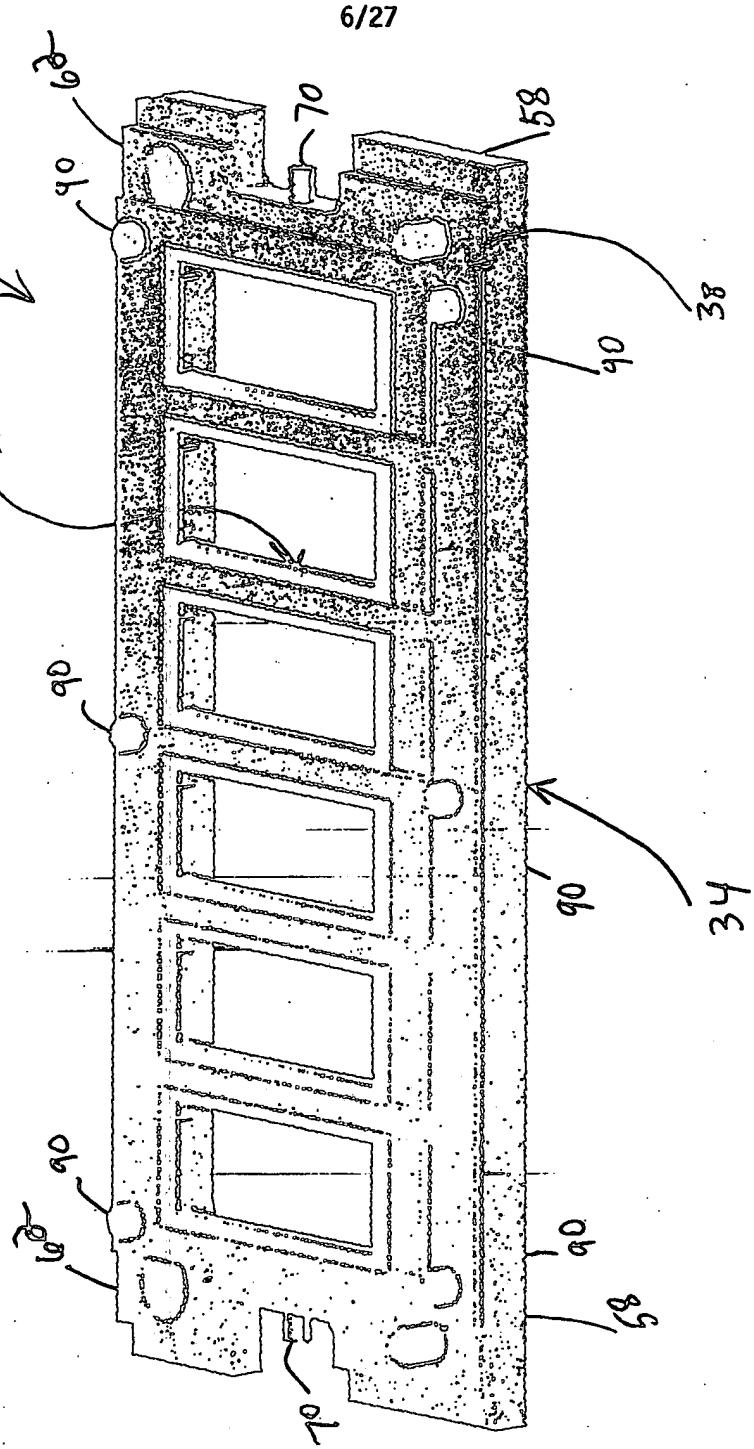

FIG. 6

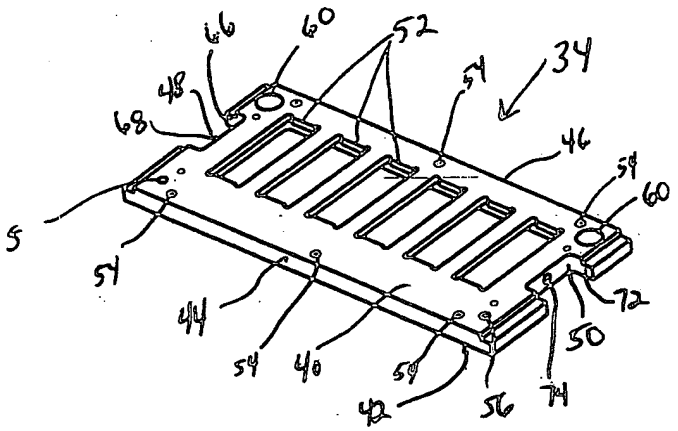

FIG. 7

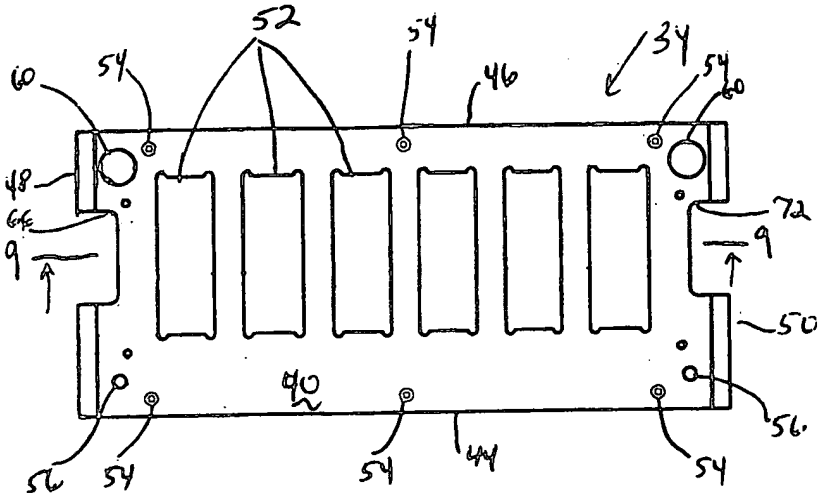

FIG. 8

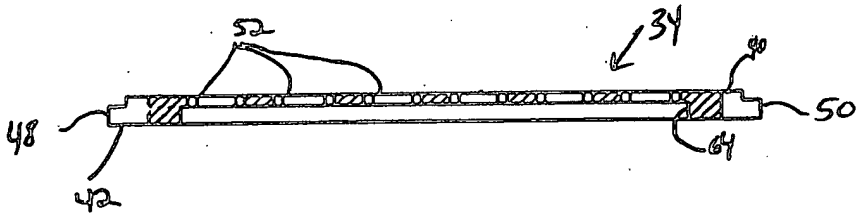

FIG. 9

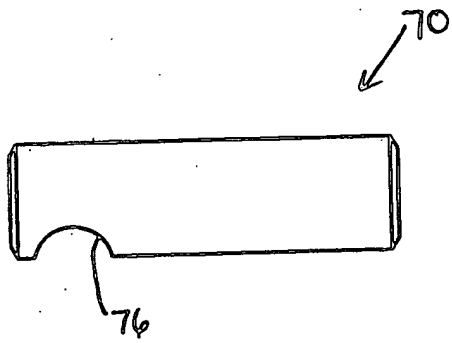

FIG. 10

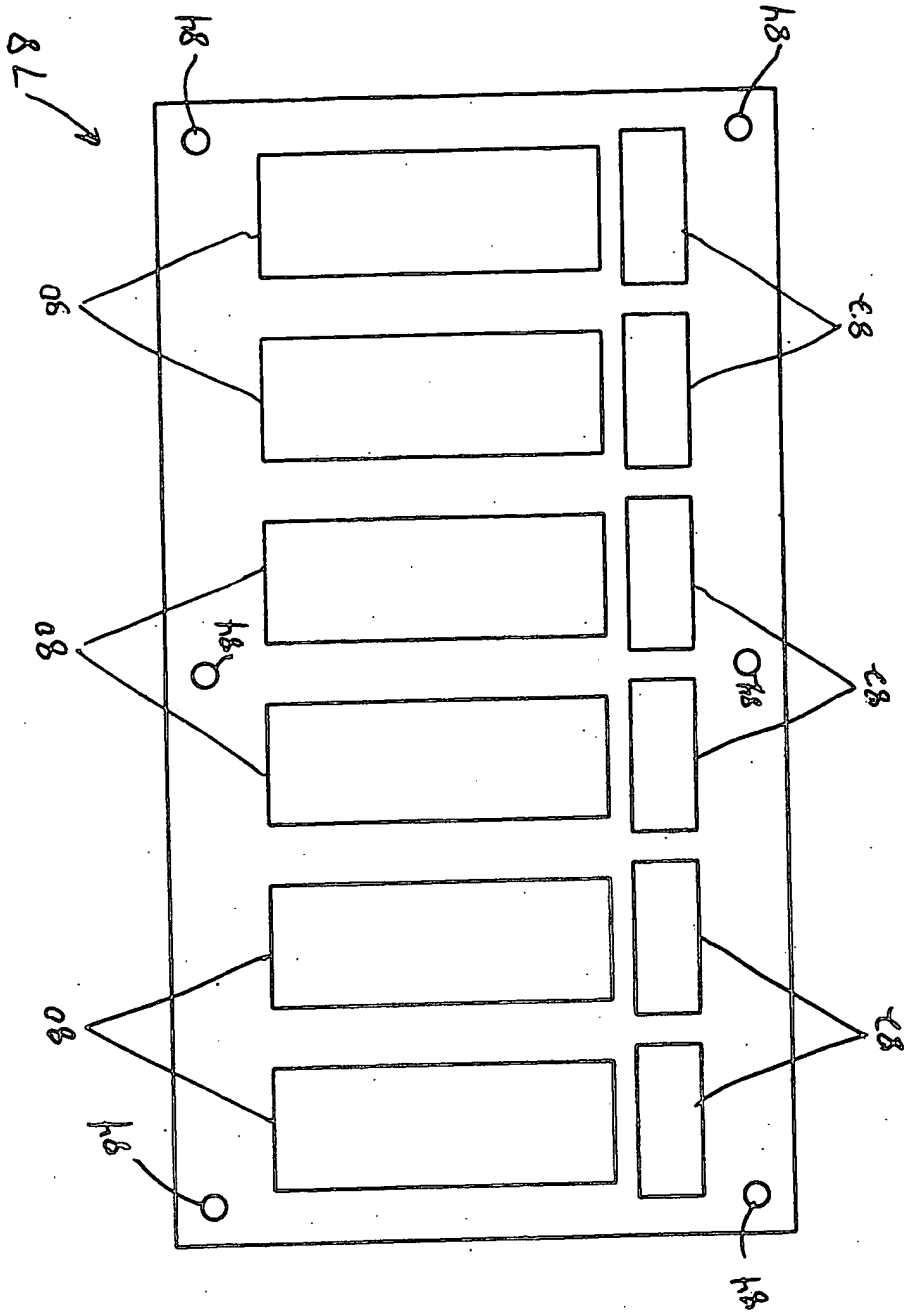

FIG. 11

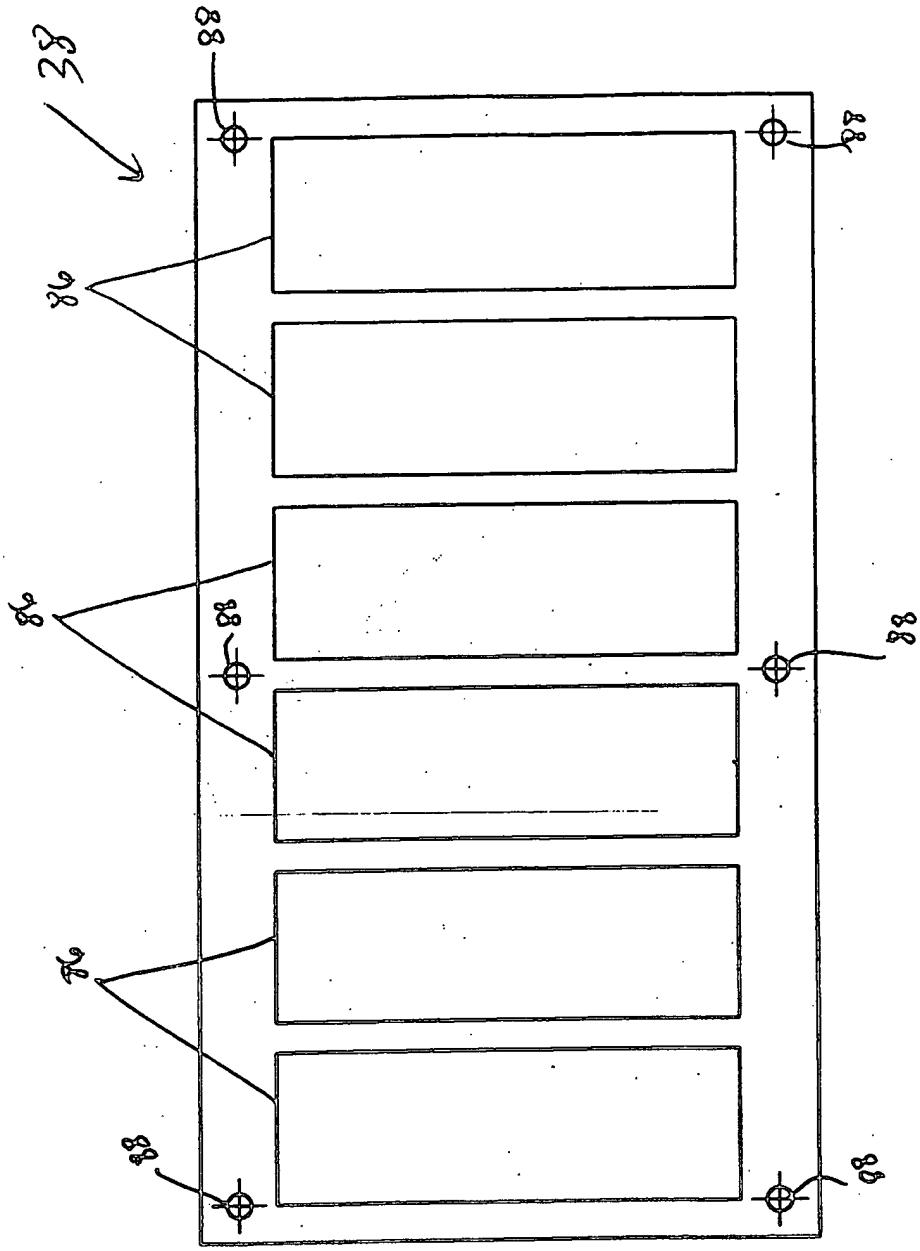

FIG. 12

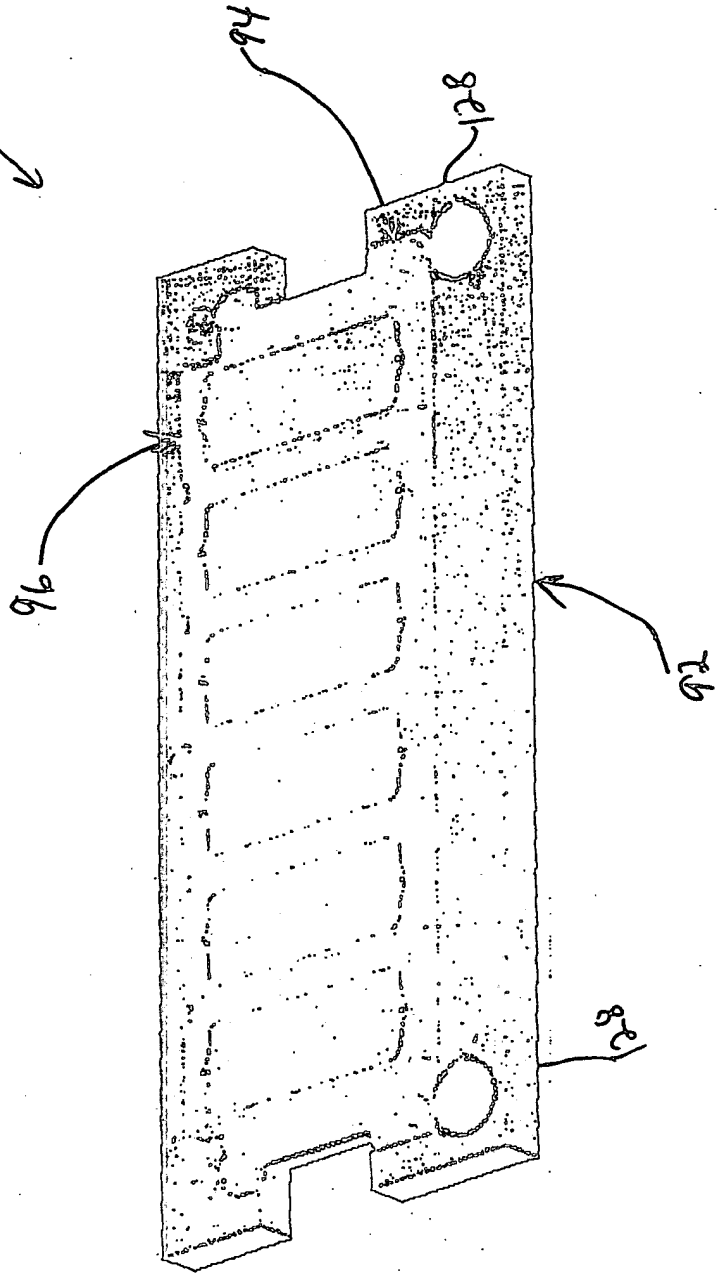

FIG. 13

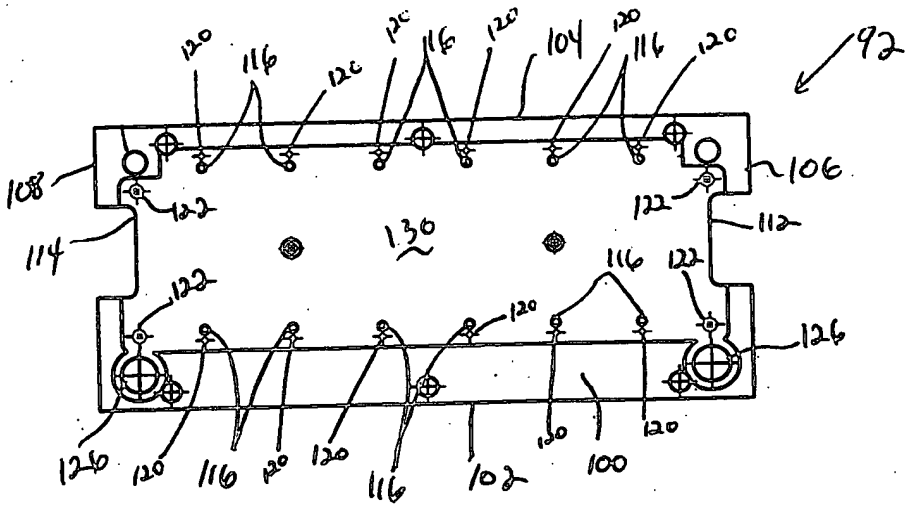
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FIG. 15

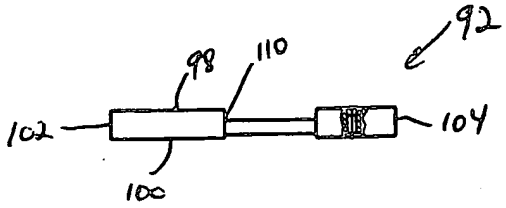

FIG. 16

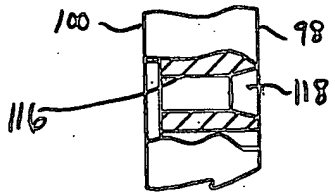

FIG. 17

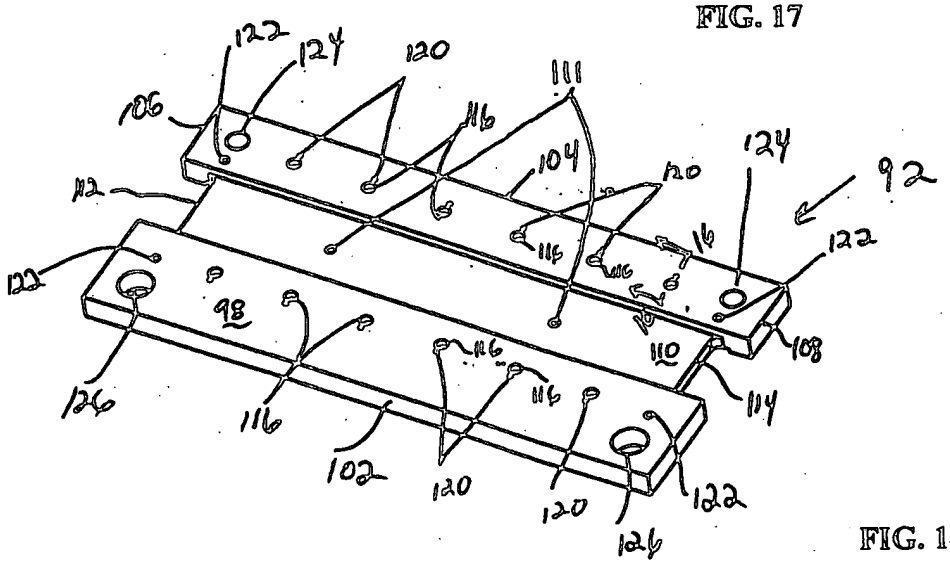

FIG. 14

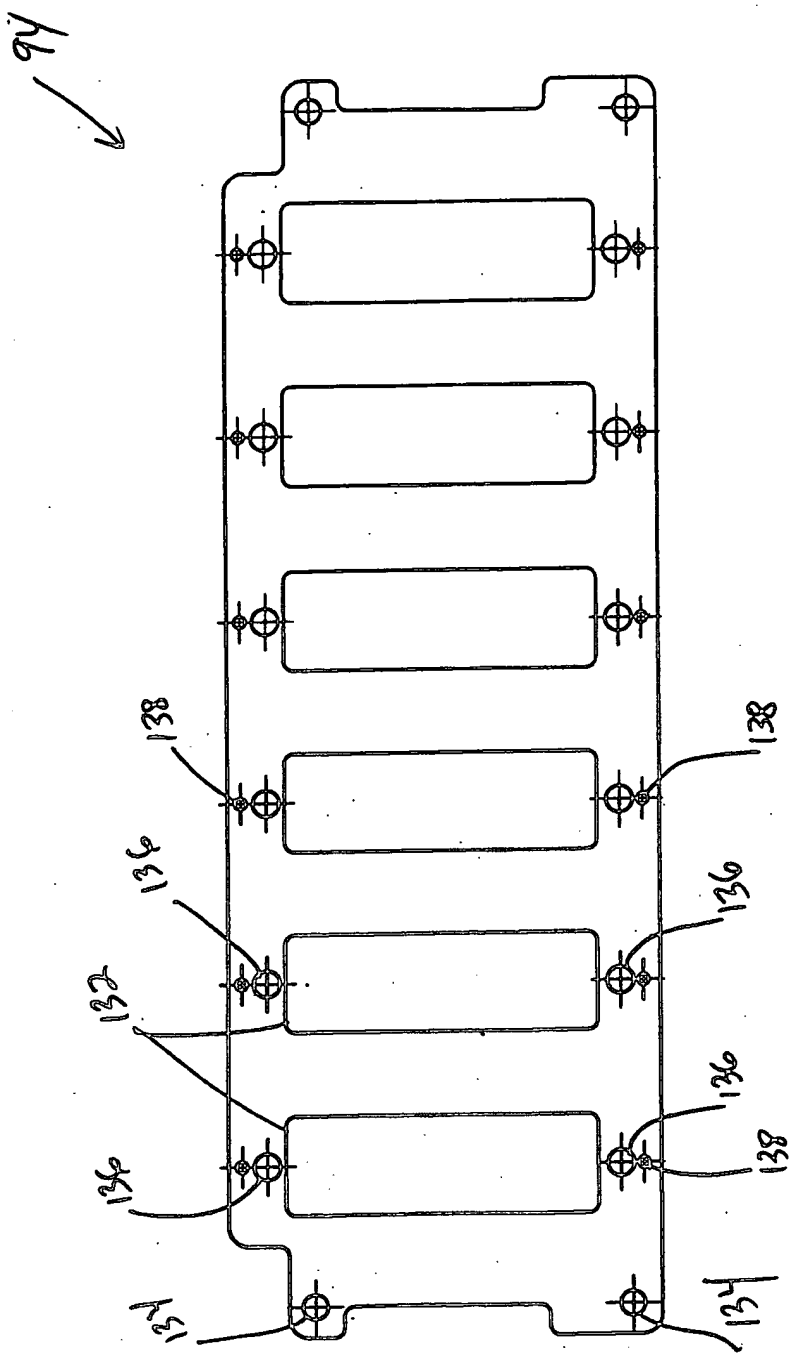

FIG. 18

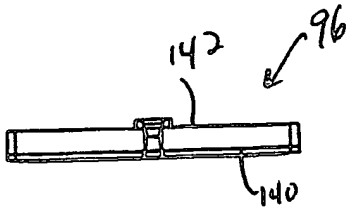

FIG. 20

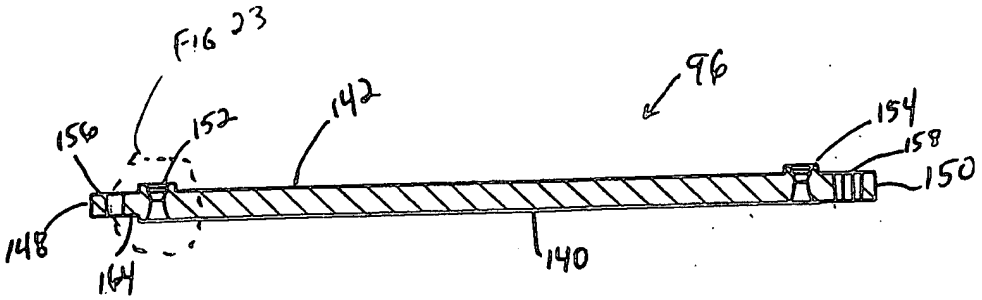

FIG. 22

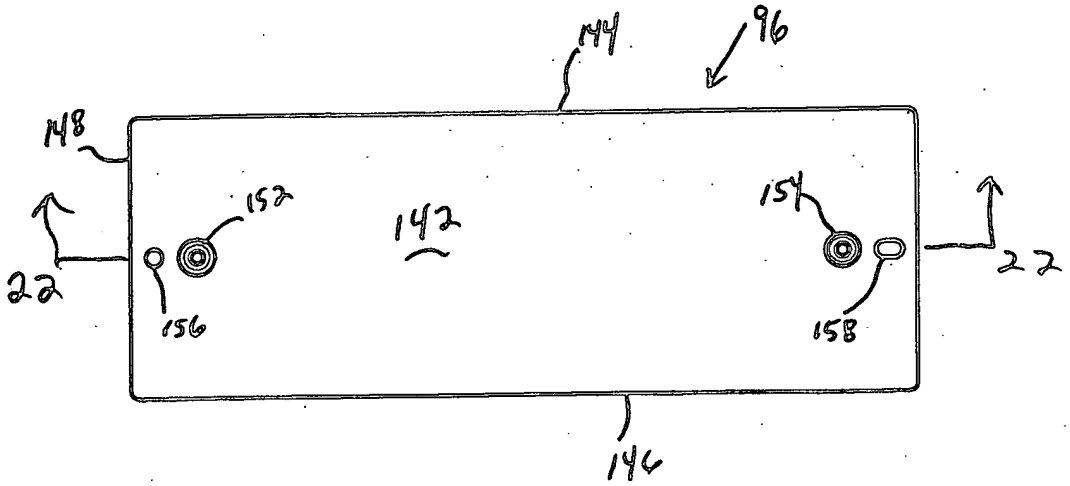

FIG. 21

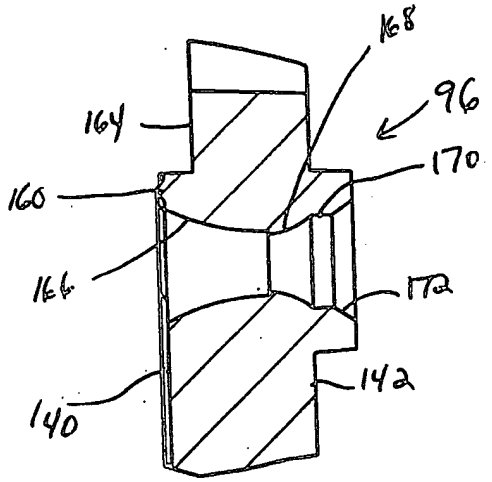
168
96
164
170
160
166
172
142
140

FIG. 23

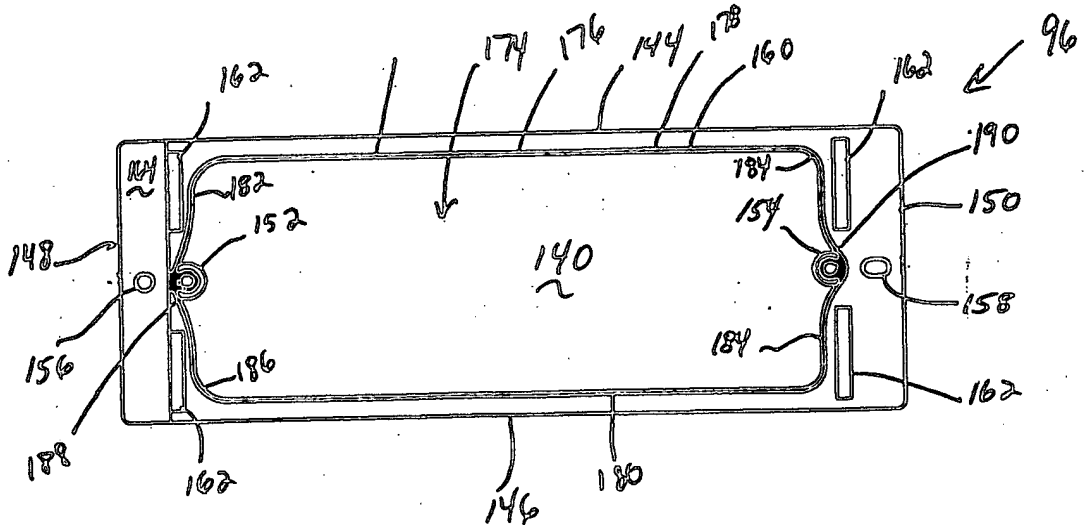
174
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FIG. 19

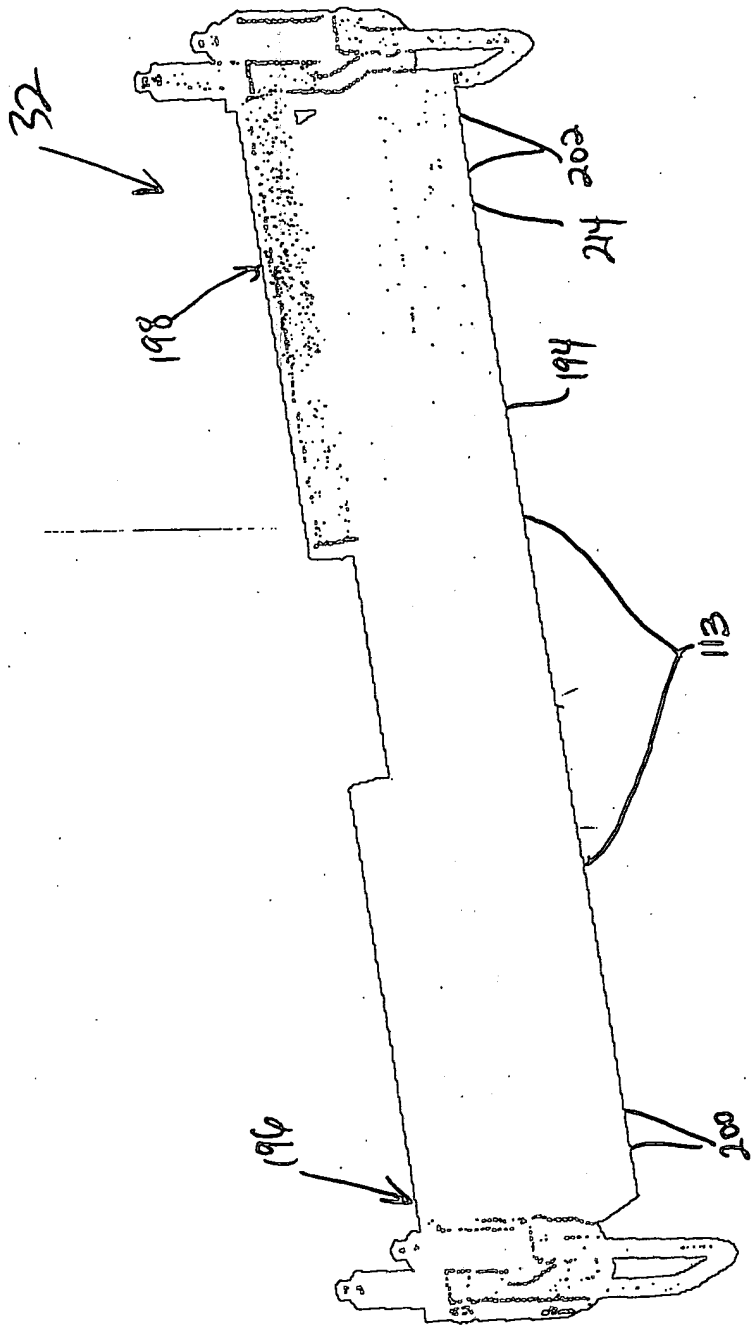


FIG. 24

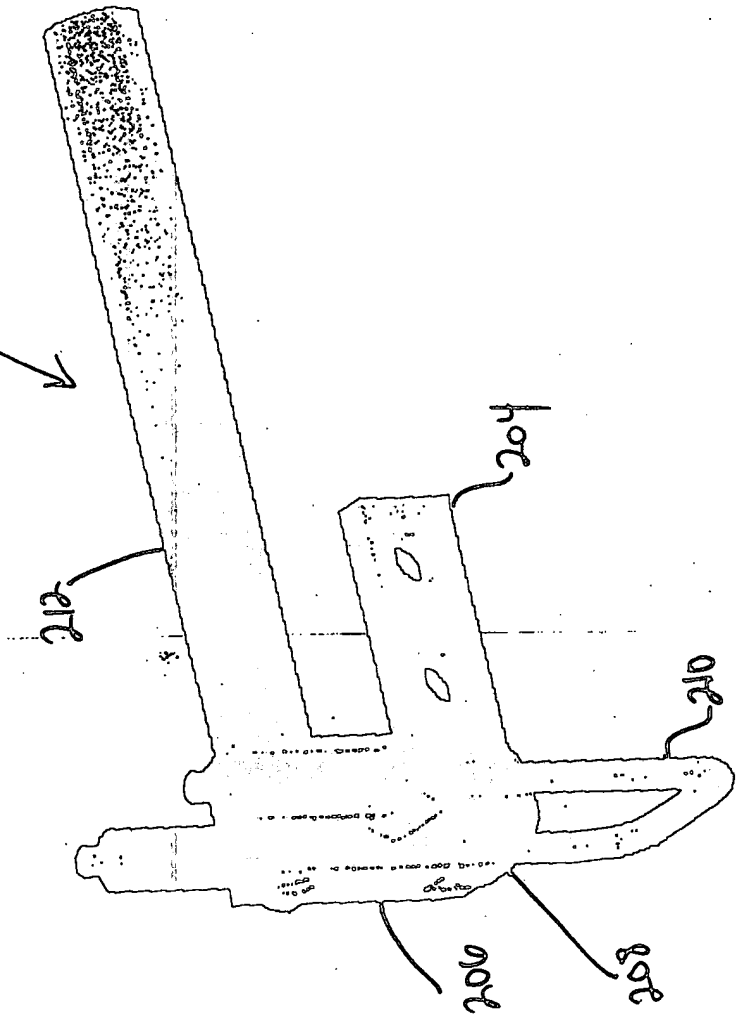


FIG. 25

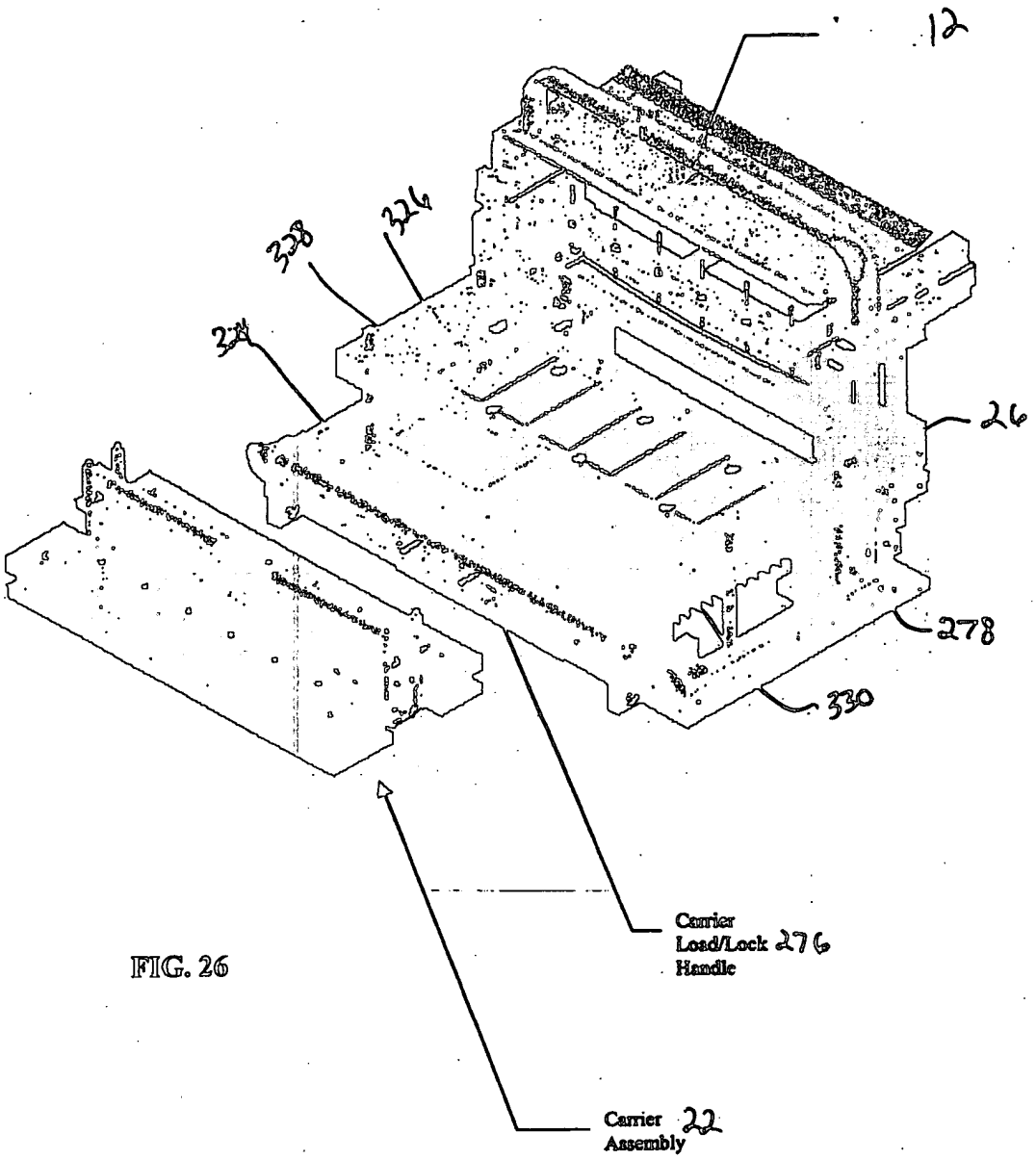

12
328
326
324
26
278
330
Carrier
Load/Lock 276
Handle
Carrier
Assembly 22

FIG. 26

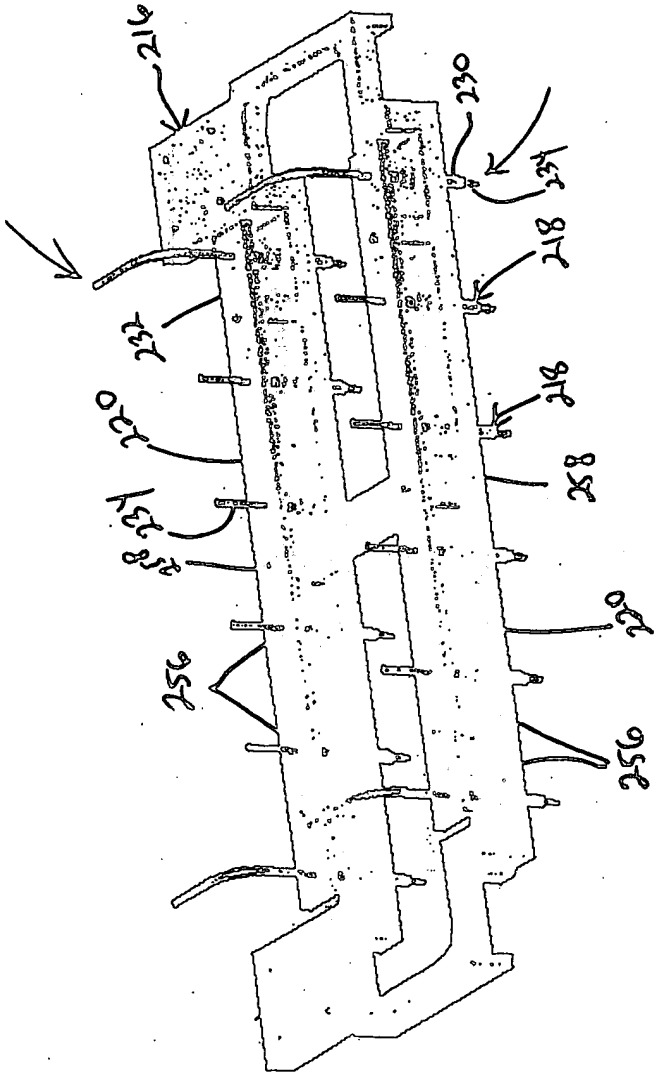
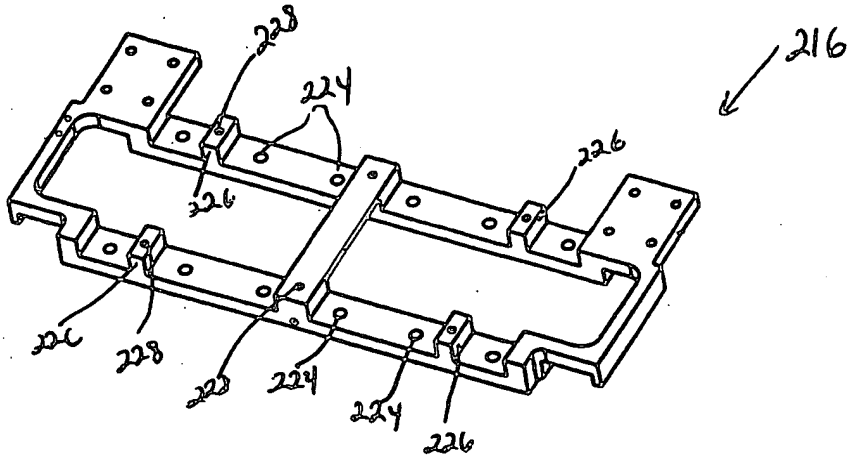


FIG. 27


228
224
216
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228
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224
226

FIG. 28

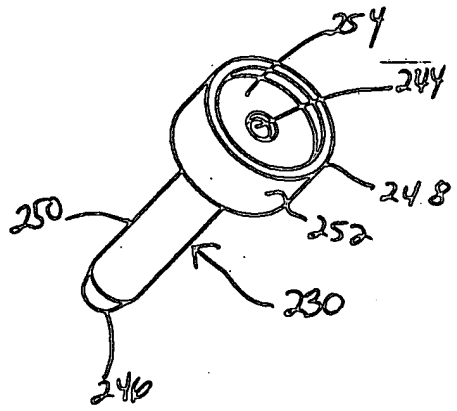

254
244
248
250
252
230
246

FIG. 30

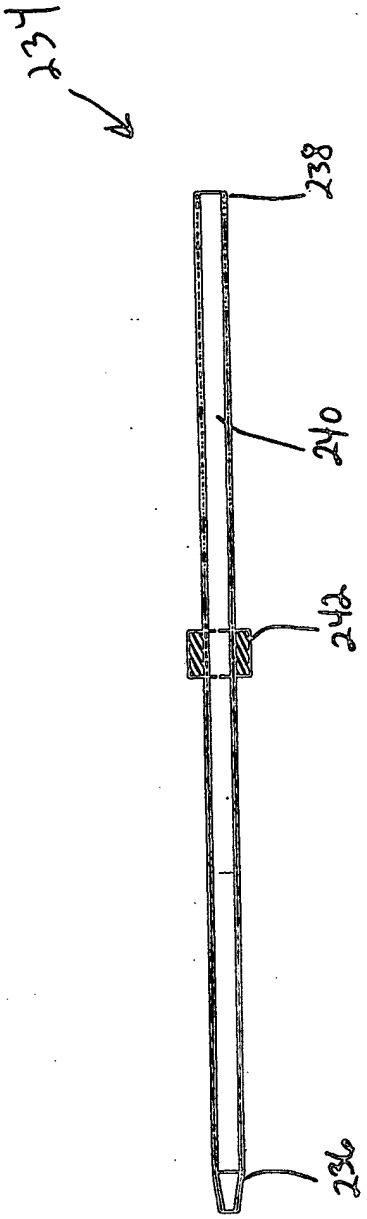


FIG. 29

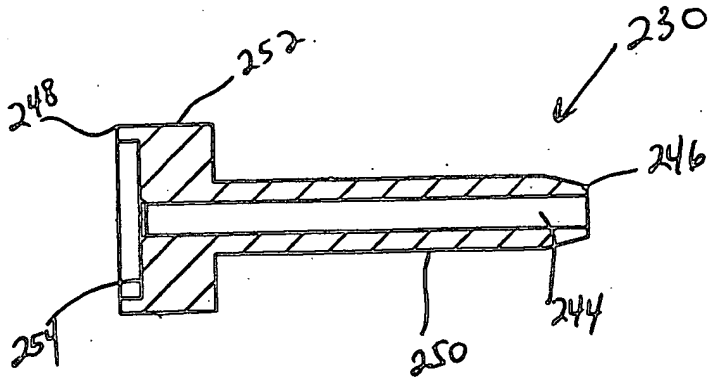


FIG. 31

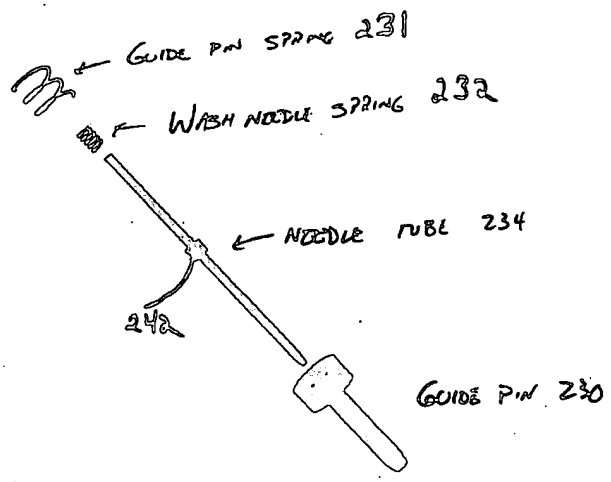

GUIDE PIN SPRING 231
WASH NOZZLE SPRING 232
NOZZLE TUBE 234
242
GUIDE PIN 230

FIG. 32

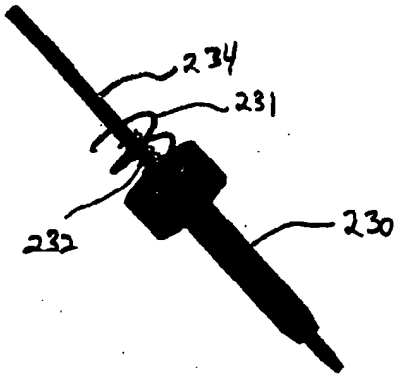


FIG. 33

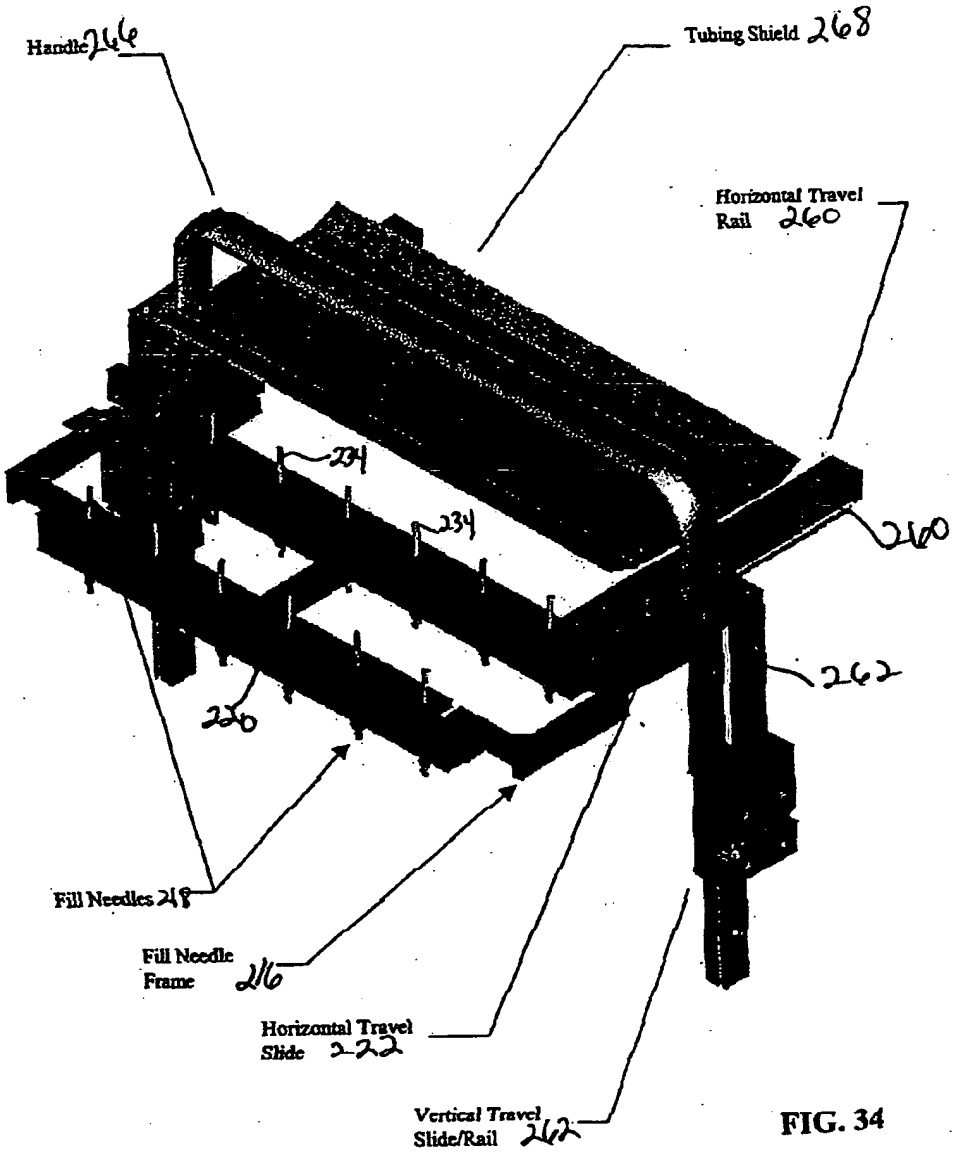

Handle 266
Tubing Shield 268
Horizontal Travel Rail 260
234
234
260
262
220
Fill Needles 218
Fill Needle Frame 216
Horizontal Travel Slide 222
Vertical Travel Slide/Rail 262

FIG. 34

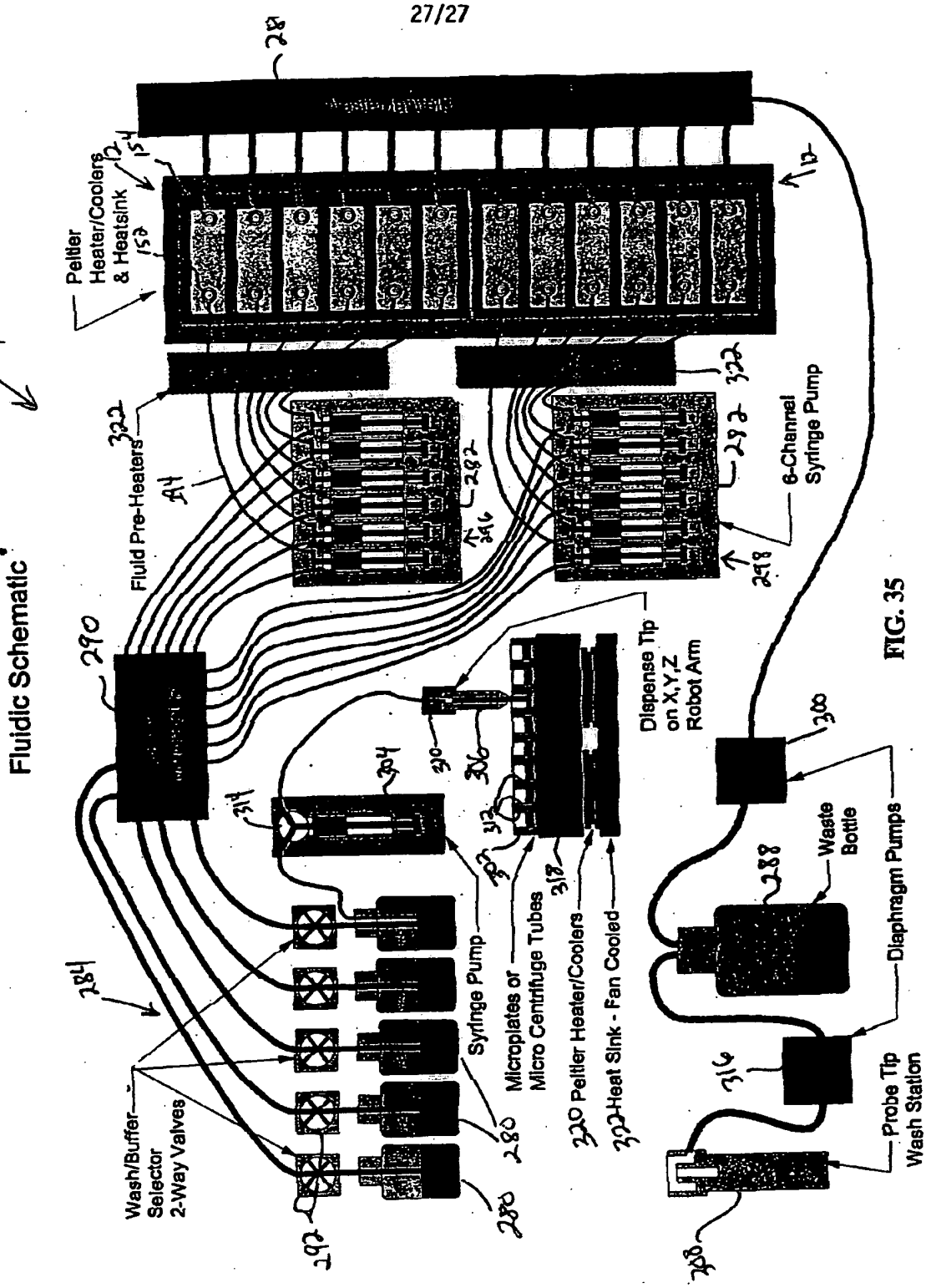

Fluidic Schematic
14
28
Peltier Heater/Coolers & Heatsink
154
152
12
322
Fluid Pre-Heaters
314
282
316
6-Channel Syringe Pump
298
290
Dispense Tip on X,Y,Z Robot Arm
310
306
304
312
302
318
300
284
Syringe Pump
Microplates or Micro Centrifuge Tubes
320 Peltier Heater/Coolers
322 Heat Sink - Fan Cooled
Waste Bottle
288
Diaphragm Pumps
Wash/Buffer Selector 2-Way Valves
280
316
Probe Tip Wash Station
308
292

FIG. 35

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/41899

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 B01L3/00 G02B21/34 C12Q1/68 B01L7/00
//B01J19/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12M B01L C12Q B01J G02B G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 93 19207 A (GENE TEC CORP) 30 September 1993 (1993-09-30) page 1, line 23 -page 2, line 9 page 4, line 7 -page 6, line 5 page 6, line 32 -page 7, line 17 page 8, line 27 -page 11, line 12 page 10, line 17 -page 11, line 12	1-3,6-9, 24,25, 30-32, 34,36, 54-56, 60,61, 63-67 48-53
Y	page 12, line 9 -page 15, line 9	10-12, 39,40, 45-47, 58,59
Y	page 16, line 31 -page 17, line 4	10-12, 39,40, 45-47,

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 September 2001	07. 01. 02

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Koch, A

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
		58,59
	page 17, line 22 -page 18, line 15 page 18, line 30 -page 19, line 29 page 20, line 26 -page 21, line 4	
Y	page 25, line 9 -page 26, line 3 figures 1-10	48-53

X	EP 0 611 598 A (PERKIN ELMER CORP) 24 August 1994 (1994-08-24)	1-6,9, 24,25, 27-31, 54,55,62
	column 2, line 18 -column 2, line 33 column 3, line 13 -column 3, line 24 column 9, line 21 -column 11, line 30 column 20, line 3 -column 20, line 55 figures 1-5,16,17	

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 00/41899

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-67

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-67

   Chamber with examination surface and chamber element, and carrier comprising this chamber, this carrier being removably insertable into a station, and method related with this device.

2. Claims: 68-92

   Hybridization station

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 00/41899

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9319207 A	30-09-1993	US 5346672 A	13-09-1994
		US 5281516 A	25-01-1994
		EP 0632839 A	11-01-1995
		US RE35716 E	20-01-1998
EP 0611598 A	24-08-1994	US 5364790 A	15-11-1994
		AT 177024 T	15-03-1999
		AU 673397 B	07-11-1996
		AU 5505494 A	18-08-1994
		AU 705036 B	13-05-1999
		AU 6219496 A	21-11-1996
		CA 2106360 A	17-08-1994
		CN 1095759 A,B	30-11-1994
		DE 69323720 D	08-04-1999
		DE 69323720 T	01-07-1999
		DK 611598 T	27-09-1999
		EP 0884394 A	16-12-1998
		IL 107131 A	30-09-1997
		IL 120847 A	22-09-1999
		JP 6245771 A	06-09-1994
		NZ 248835 A	21-12-1995
		US 5527510 A	18-06-1996
		US 5675700 A	07-10-1997
		US 5681741 A	28-10-1997

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
10 May 2001 (10.05.2001)

PCT

(10) International Publication Number
WO 01/032934 A3

(51) International Patent Classification[7]: B01L 3/00, G02B 21/34, C12Q 1/68, B01L 7/00 // B01J 19/00

(21) International Application Number: PCT/US00/41899

(22) International Filing Date:
3 November 2000 (03.11.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/163,634 4 November 1999 (04.11.1999) US

(71) Applicant (for all designated States except US): ARCTURUS ENGINEERING, INC. [US/US]; 400 Logue Avenue, Mountain View, CA 94043 (US).

(72) Inventors; and
(75) Inventors/Applicants (for US only): BAER, Thomas, M. [US/US]; 537 Drucilla Drive, Mountain View, CA 94040 (US). RICHARDSON, Bruce, J. [US/US]; 14801 Golf Links Drive, Los Gatos, CA 95032 (US). KITAZAWA, Chris, T. [US/US]; 3075 Woodcrest Drive, San Jose, CA 95118 (US). BERNS, Darren [US/US]; 2071 Emerald Drive, Longmont, CO 80504 (US). MORAVICK, Keith, E. [US/US]; 971 Maddux Drive, Palo Alto, CA 94304 (US). JOHNSON, Bruce, A. [US/US]; 2250 #2 Latham Street, Mountain View, CA 94040 (US). SCHENCK, Alan, L. [US/US]; 1784 Kimberly Drive, Sunnyvale, CA 94087 (US). BARKER, Craig, S. [US/US]; 410 De Anza Avenue, San Carlos, CA 94070 (US).

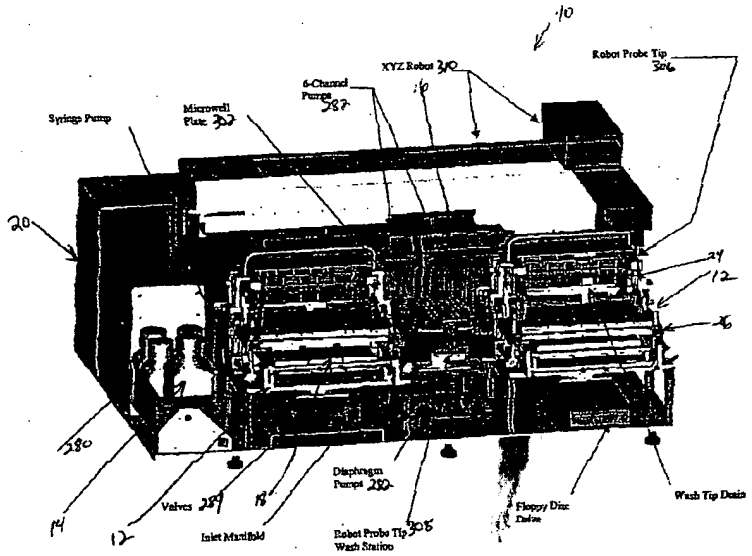
(74) Agents: LUKAS, Rimas, T. et al.; Morrison & Foerster LLP, 755 Page Mill Road, Palo Alto, CA 94304-1018 (US).

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian

[Continued on next page]

(54) Title: HYBRIDIZATION STATION



(57) Abstract: This invention provides a station for rapidly preparing arrayed slides for hybridizations. At least one micro-arrayed slide is inserted into a carrier. A hybridization chamber is formed by a chamber element contacting the slide. The carrier is removably insertable into the station for the carrying out of various steps associated with the pre-hybridization and post-hybridization processes. The station generally includes at least one wash station assembly, a fluid delivery system, a sample delivery system, and a temperature control system.

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